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Cancer-Symptom Burden and Health-Related Quality of Life Associated with Sleep Disturbance and Hypnotic Use

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Cancer-Symptom Burden and Health-Related Quality of Life Associated with Sleep Disturbance and Hypnotic Use

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Objectives: To assess prevalence and correlates of cancer-related sleep disturbance (SD) and hypnotic use, and evaluate changes in cancer symptom burden and health-related quality of life (HRQoL) associated with sleep disturbance change and hypnotic use.

Methods: Secondary analysis of the Symptom Outcomes and Practice Patterns (SOAPP) survey of 3,106 adult (aged ≥ 18 years) outpatients receiving treatment for breast, lung, prostate, or colorectal cancer between March 3, 2006 and May 19, 2008. At baseline and approximately four weeks later, patients scored severity of nineteen cancer symptoms from 0='Not present' to 10='As bad as you can imagine'. Both patients and clinicians scored symptom-burden interference for six HRQoL items (from 0='Did not interfere' to 10='interfered completely'). Correlates of SD and hypnotic use were identified using linear and logistic regression, respectively. Multivariate analyses tested whether hypnotic use (Hotelling's T^2) or change in SD severity (multivariate linear regression) were associated with changes in symptom burden and HRQoL. Cancer-specific subgroups were evaluated when sample size permitted.

Results: SD scores were available for 2,748 participants: 71% female, 86% white, mean age 61 years (range, 23-93 years). Primary cancer sites: breast (51%), colorectal (24%), lung (15%), and prostate (10%). The majority (62.8%) reported SD and 23.5% used hypnotics. The most important SD correlates were other cancer symptoms, regardless of their severity. Distress was the strongest and only universal correlate; cognitive difficulty, drowsiness, and fatigue were also common across cancer-specific subgroups. Hypnotic use was two to three times higher among whites, versus blacks. Several sedating medications correlated positively with hypnotic use, including opioid analgesics and promethazine. Hypnotic use correlated positively with clinician-identified distress, but not with clinician-identified sleep disturbance. Reduced sleep disturbance severity (SDS) correlated with improvement in nearly all symptoms (most notably: distress, dry mouth, and fatigue), and with improved HRQoL (possibly mediated by other symptoms). Hypnotic use correlated modestly with lower overall symptom burden, but not HRQoL change.

Conclusions: Relationships observed between SD and many other cancer symptoms argue in favor of therapies that target multiple symptoms. Patterns of hypnotic use raise questions about whether cancer-related SD is being treated adequately, equitably, and effectively.

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Chapter 1: Background and Literature Review

This chapter provides a discussion of background literature relevant to the present study, beginning with an overview of sleep disturbance in general, including definitions, risk factors, and clinical implications. This is followed by a brief summary of literature characterizing sleep disturbance in the oncology setting, including prevalence and oncology-specific risk factors, available treatments, evidence relating to use of those treatments in people with cancer. (For a detailed treatment of these topics, please refer to the previously published works listed below.) The chapter closes with a statement of rationale for the proposed study.

For more detail on pharmacotherapies for insomnia and insomnia in the setting of cancer, please refer to these previously published works.

Scalo JF, Rascati KL. Pharmacotherapy for Insomnia. In: McCall WV, ed. *Advances in the Management of Primary and Secondary Insomnia*. London, UK: Future Medicine; 2014:72-90. [The first author was the primary author.]

and

Scalo JF, Rascati KL. Insomnia in the Setting of Cancer. In: McCall WV, ed. *Advances in the Management of Primary and Secondary Insomnia*. London, UK: Future Medicine; 2014:32-54. [The first author was the primary author.]

1.1 Section I: Overview of Sleep Disturbance

Sleep is essential for health and well-being, and it is well established that sleep disturbance is associated with numerous physiological and psychological impairments. Sleep disturbance is also costly; poor sleep increases patients' medical expenditures and decreases productivity at work and school. This section provides a brief overview of the characterization and measurement of sleep disturbance, risk factors and epidemiology, and associated clinical and socioeconomic outcomes.

1.1.1 Defining sleep disturbance

The terms *sleep disturbance* and *insomnia* are often used interchangeably to describe difficulty falling asleep, staying asleep, and / or dissatisfaction with the quality of one's sleep. Diagnostic criteria for insomnia, however, are more specific and require the presence of daytime symptoms that reflect the pathologic effects of disturbed sleep.

The International Classification of Sleep Disorders, Third Edition (ICSD-3)[1] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[2] define insomnia as sleep difficulties that occur at least three nights per week for at least three months, and that are accompanied by daytime sequelae such as fatigue, memory impairment, irritability, sleepiness, or impaired performance at work or school. These diagnostic criteria have been in flux over recent years, and in research literature the operational definitions of sleep disturbance vary considerably. For the purposes of this work, the term *sleep disturbance* is used as a generic term for difficulty sleeping and does not reflect a particular definition or set of diagnostic criteria. The term *insomnia* will be used to identify cases in which disturbed sleep is known to be accompanied by related daytime dysfunction.

1.1.2 Measuring sleep disturbance

A variety of instruments are available to assess patients' subjective experience of sleep disturbance, including the Pittsburgh Sleep Quality Index, the Insomnia Severity Index, and the Epworth Sleepiness Scale.[3] Objective measurements are also possible using sleep actigraphs and polysomnography. Sleep actigraphs are small accelerometer-containing devices that record motion. Generally worn on the wrist, an actigraph collects information that indicates a patient's sleep/wake cycles as well as the level of arousal or activity during sleep.[4] Polysomnography provides comprehensive reporting of internal physiological activity during sleep with electrical field recordings of the brain (electroencephalogram), eyes (electro-occulogram), skeletal muscles (electromyogram), and heart (electrocardiogram).[4]

Actigraphy is commonly used in the diagnosis of insomnia,[3] as it is relatively easy and economical, and can provide measurements for several sleep parameters of clinical interest, including:

- Sleep onset latency (SOL): time elapsed between bedtime and sleep onset
- Wake time after sleep onset (WASO)
- Number of awakenings
- Total sleep period: time from initial sleep onset to final awakening
- Total sleep time (TST): actual time spent asleep, not including waking episodes
- Sleep efficiency: the ratio of total sleep time to total sleep period

Polysomnography is not routinely used for diagnosis of insomnia, unless there is reason to suspect an additional sleep disorder (e.g., sleep apnea or movement disorders), but is used extensively in sleep research. From polysomnography recordings, investigators have discovered that sleep occurs in phases, or stages. The two main phases of sleep are the rapid eye movement (REM) phase and the non-rapid eye movement (NREM) phase.[5] NREM sleep can be further divided into stages S1 through S4. Humans typically cycle through all four stages of NREM plus the REM stage five or six times nightly, with each cycle lasting about 90 minutes.[6] Sleepers in stages S1 and S2 exhibit high frequency brain-wave activity and are relatively easy to awaken (lighter sleep), while sleepers in stages S3 and S4, referred to collectively as delta phase or slow wave sleep (SWS), exhibit low frequency cortical waves and are more resistant to being awoken (deeper sleep).[7]

1.1.3 Risk factors for sleep disturbance

Sleep disturbance may be attributable to a number of factors. Often, sleep disturbance is secondary to mental disorders (e.g., depression, anxiety, Alzheimer's disease, or schizophrenia), or may result from physical conditions, such as chronic pain, cancer, sleep apnea, or restless legs syndrome.[8] Some patients suffer from circadian disorders, in which hormonal timing of sleep cycles are disrupted,[9,10] and shift-workers commonly experience difficulty achieving restorative sleep during daylight hours.[11] There are many medications that can interfere with sleep,[12] as can environmental conditions, including noises and uncomfortable temperatures.[13] Stressors that commonly contribute to insomnia include work-, family-, and school-related problems.[14] In 1987, Spielman, Caruso, and Glovinsky proposed what is now called the 3P model, which classifies risk factors as having predisposing, precipitating, and/or perpetuating effects on the development of insomnia. For example, individuals who tend to experience high levels of anxiety and worry may be predisposed to experience disrupted sleep in response to a stressful life event.[15,16] Acute disruptions to sleep may be precipitated by events such as job loss, new onset of a medical condition, birth of a child, or death of loved one.[14] As the precipitating event resolves, or as the individual adjusts, normal sleep should return. Chronic insomnia may develop, however, in the presence of perpetuating factors. Sustained or repeated exposure to life stress can result in conditioned somatic (bodily) and cognitive hyperarousal,[17] characterized by increased metabolic rates, elevated temperature and heart rate, and increased cortisol secretion due to activation of the hypothalamic-pituitary-adrenal axis.[18] Maladaptive behaviors, such as remaining in bed despite failure to fall asleep, and worrying excessively about not sleeping, may also engender cognitive and/or psychological hyperarousal at bedtime.[17]

1.1.4 Genetics of sleep disturbance

Particular genetic risk factors for sleep disturbance have yet to be identified, but studies have discovered a high degree of familial aggregation among first-degree relatives with insomnia, which provides strong evidence of a genetic contribution to etiology.[14,19,20] Further investigation is needed, however, including genome-wide association studies (GWASs) to search for genetic regions linked with particular sleep disturbance symptoms. Two such studies have found that subjects with insomnia share genotypic differences in regions thought to be involved in the regulation of circadian rhythms.[21,22] Another GWAS has identified three genes that may associated with sleep duration (statistical significance cutoff was not met). For one of these, KLF6, expression was observed to be higher in subjects whose sleep was restricted during the study, suggesting that sleep may alter gene expression and *vice versa*.[23] More recently, a meta-analysis of GWASs identified an association between sleep latency and three variants of the gene RBFOX3; the authors predict, based on analysis of co-expression with other genes, that RBFOX3 plays a role in the release of neurotransmitters that trigger sleep onset.[24]

Better understanding of the genetics of sleep can help to identify novel targets for pharmacotherapy. In addition, insight into the complex interplay of sleep with other homeostatic systems could inform development of behavioral and environmental interventions to improve sleep. There is still much to learn, however, about the precise genes involved as well as their functions. Furthermore, genetic risk factors for insomnia are likely to be manifold, so genome-wide searches for other insomnia-related characteristics should be continued.

1.1.5 Epidemiology of sleep disturbance

Between one-third and one-half of US adults experience sleep disturbance, and about one in five (22%) also suffer from daytime sequelae such as fatigue, motor incoordination, and impaired cognition.[25-27] Sleep disturbances are more common among women, and prevalence increases with age. Before the age of 46 years, women are 1.4 times more likely than men to experience insomnia; the risk ratio increases to 1.7 after age 46.[28] Reports of difficulty maintaining sleep are more frequent in adults aged 65 years and older, but it remains unclear to what extent this increase is due to changes in sleep itself, increased prevalence of comorbid conditions that may interrupt sleep, or lifestyle factors that contribute to perceived satisfaction with sleep.[27-31] Lower socioeconomic status is also associated with higher prevalence of insomnia, but conflicting results from multivariate analyses indicate that this relationship may reflect some other common cause (or causes).[28] Finally, prevalence of insomnia appears to vary with race/ethnicity, but the literature is limited and somewhat mixed.

Studies evaluating the prevalence of insomnia among different racial/ethnic groups have primarily focused on comparisons between whites and blacks. Several studies found that blacks take longer to fall asleep, sleep for shorter periods of time, and report less satisfaction with sleep than whites.[32-38] Interestingly, there appears to be an age by race interaction, with reports of insomnia increasing among older whites, but decreasing among older blacks.[39] Further investigation into this effect is needed, however, as it may reflect social coping mechanisms (e.g., withholding complaints to be socially acceptable, or acceptance of hardships over a lifetime), rather than a true difference in prevalence.[39,40] Regarding other racial/ethnic groups, the literature is scant and more research is needed, but there is some evidence that Native Americans and Hispanics have more difficulty sleeping than whites, while Asian Americans appear to experience sleep disturbance at rates similar to whites in the US.[34,36,37,41]

1.1.6 Clinical implications of sleep disturbance

Although there is still much to learn about the various functions of sleep, there is evidence that important physical and mental processes take place during this time. It is thought that physical restoration occurs during SWS, which is accompanied by the release of growth hormone and an increase in anabolic (tissue-building) activity.[42] Sleep deficits, on the other hand, are accompanied by detrimental metabolic changes, including impaired glucose tolerance, up-regulated appetite, and decreased energy expenditure.[43] Lack of sleep can disrupt regulation of the immune system, with effects such as increased production of inflammatory cytokines, increased C-reactive protein (a marker of inflammation), and decreased immune cell response.[44-47]

Sleep is also considered essential for cognitive function. Memory consolidation (reinforcement) is thought to occur during REM and NREM stages of sleep,[48] and clearance of neurotoxins from the cerebrospinal fluid increases dramatically during sleep. Lymphatic vessels, which transport toxic metabolic waste products from peripheral tissue, are not present in the central nervous system. Instead, neuronal metabolites are flushed from cerebrospinal fluid into interstitial fluid via hydrodynamic changes meditated by glial cells.[49] That this process, termed the *glymphatic system,* is suppressed during the awake state helps to explain the restorative effects of sleep.[50] Polysomnography studies confirm that insomnia sufferers spend less time in SWS, which likely explains their complaints of next day fatigue and cognitive difficulties.[51]

Patients who chronically experience disturbed sleep are at increased risk for developing a wide range of illnesses, including anxiety and/or depression,[52-55] alcohol abuse,[56] hypertension,[57] stroke,[58] diabetes,[59] obesity,[59,60] and cancer.[61] In light of these far-reaching effects, it is not surprising that several investigations have confirmed an association between sleep disturbances and reduced quality of life.[62-69] In a recent study of the association between insomnia and health-related quality of life (HRQoL) in a large, nationally representative sample, reduced HRQoL scores were observed in both the physical and mental domains for persons with diagnosed insomnia.[70]

1.1.7 Socioeconomic burden of sleep disturbance

The socioeconomic cost of sleep disturbance is mediated by effects in many domains, including exacerbation of other disease states, increased risk of motor-vehicle accidents, and decreased workplace productivity.[71,72] Sleep disturbance may itself be a risk factor for poor economic status, as workers with disturbed sleep experience increased odds of negative work outcomes, including decreased concentration and productivity, and increased absenteeism and accidents.[73] A few studies have attempted to quantify the economic impact of insomnia, but updated research is needed. These studies, by different researchers using various methods and data sources, all confirmed that costs related to sleep disorders in the US are substantial. Specifically, estimates were: $11.96 billion [US$1995] for outpatient visits, $1.97 billion [US$1995] for medications, $41.1 billion [US$1994] for lost productivity, and between $43.15 and $56.02 billion [US$1988] for accidents, but these studies are all prior to 2000.[74-76] The most recent studies are from Ozminkowski and Wang, who found that sleep disturbances increased patients' costs by about $1200 [US$2003] yearly,[77] and Pollack et. al., who estimated yearly increased healthcare and productivity costs of $858 [US$2002-2003] per patient.[78]

1.1.8 Treatment of sleep disturbance

Guidelines form the American Academy of Sleep Medicine list cognitive and behavioral therapies, such as biofeedback or relaxation therapy, as first-line choices for treatment of insomnia.[3] Short-term pharmacotherapy may also be used, preferably supplemented with cognitive or behavioral therapy.[3] These therapies are discussed in detail in the following publication: Scalo JF, Rascati KL. Pharmacotherapy for Insomnia. In: McCall WV, ed. *Advances in the Management of Primary and Secondary Insomnia*. London, UK: Future Medicine; 2014:72-90.

1.1.9 Sleep disturbance and cancer

In the context of cancer, sleep is especially important. Patients who have difficulty sleeping experience increased frequency and severity of cancer pain and fatigue,[79-83] and are at increased risk for anxiety and depression. The effects of disturbed sleep on immune, metabolic, and other homeostatic systems not only hinder patients' recovery, but may also promote cancer progression.[61,84,85] Patients experiencing disturbed sleep report poorer quality of life[79,86,87] and often have worse prognoses.[88,89] Unfortunately, disturbed sleep is among the most common and severe symptoms reported by patients with cancer.[90]

1.2 SECTION II: SLEEP DISTURBANCE IN THE CONTEXT OF CANCER

For additional detail on this topic, please see: Scalo JF, Rascati KL. Insomnia in the Setting of Cancer. In: McCall WV, ed. *Advances in the Management of Primary and Secondary Insomnia*. London, UK: Future Medicine; 2014:32-54.

1.2.1 Prevalence of sleep disturbance in cancer

Numerous studies have assessed the prevalence of insomnia and/or sleep disturbance in the setting of cancer, but results vary widely, with estimates ranging from fewer than 20% (in a sample of 300 women treated with radiotherapy for non metastatic breast cancer)[84] to more than 90% (in a sample of 102 adults receiving palliative treatment for advanced cancer)[91] of patients. Inconsistency in published estimates is partially due to variations in study designs, including differences in the way sleep disturbance is defined and measured, the type and stage of cancer studied, and study design and methodology.

A few large studies have estimated sleep disturbance prevalence in samples representing multiple cancer types. In a mixed sample (in terms of cancer sites, as well as progression, and treatment; N=982) surveyed by Davidson et. al. (2002), 31% of participants reported insomnia symptoms.[89] Stepanski et. al. (2009) found that 55% of participants undergoing cancer treatment (N=11,445) had trouble sleeping, and 26% classified their sleep troubles as moderate to severe.[81] In a sample of participants receiving chemotherapy for cancer (N=823), Palesh et. al. (2010) found that 81% reported disturbed sleep and 43% met the diagnostic criteria for insomnia.[80] Savard et. al. (2011) surveyed patients with a first diagnosis of non metastatic cancer (N=991) scheduled for curative surgery; 31% reported sleep disturbance, and 28.5% met the diagnostic criteria for insomnia.[92] Most recently, Romito et. al. (2014) classified 66% of chemotherapy recipients (N=403) as bad sleepers.[93]

Correlates of sleep disturbance were evaluated in most of these prevalence studies, but the set of variables in each was fairly limited and there was little overlap between studies. Furthermore, only Davidson et. al. (2002) and Stepanski et. al. (2009) captured multiple stages of cancer and modes of cancer treatment. The variation across these studies complicates the interpretation and synthesis of their findings. Nonetheless, from these and other studies, a number of potential risk factors for sleep disturbance have been identified.

1.2.2 Risk factors for sleep disturbance in cancer

Simply receiving a cancer diagnosis may precipitate nearly half of all cases of insomnia,[88,89] and existing insomnia can increase in severity after diagnosis.[61,84,85] Inflammation, a hallmark of cancer,[94-96] causes pain, cognitive impairment, and general malaise that can interrupt sleep,[97] and is also observed to disrupt normal sleep architecture.[98-100] Drugs and procedures used to treat cancer (or its symptoms) can also contribute to disturbed sleep.[92,101,102] Severe and persistent circadian rhythm disruptions have been observed in patients receiving chemotherapy,[103] and evidence is emerging that certain chemotherapeutic agents may increase the production of pro-inflammatory cytokines by immune cells.[104] Corticosteroids are used extensively in the setting of cancer to control nausea, prevent or treat hypersensitivity reactions to infusions, decrease pain, increase appetite, reduce inflammation, and even as a component of chemotherapy, but their excitatory effects on the central nervous system can substantially interfere with sleep.[105] When hospitalized, patients must endure noises, lights, discomfort, and interruptions by medical personnel,[106] and for patients with advanced cancer, the onset of delirium late in the day can substantially disrupt sleep.[107] Sleep is also made more difficult as a result of the many symptoms experienced by persons with cancer, including fatigue, pain, nausea, and vomiting.[92,108-110]

1.2.3 Consequences of sleep disturbance in cancer

Disturbed sleep can reduce health-related quality of life for persons with cancer,[87,91,111] and may even worsen prognosis.[88,89] Disruptions to sleep can decrease pain thresholds in healthy patients,[112] and, for patients already in pain, a poor night's sleep can increase next-day pain intensity.[113] Similarly, sleep disturbance also often occurs together with, and may have reciprocal relationships with fatigue[114-117] and depression.[118,119] Certain symptoms have been observed to occur together with such frequency that they are identified as *symptom clusters*. Identification of symptom clusters has clinical relevance, because there is evidence that symptom clusters synergistically affect outcomes in persons with cancer. For example, the independent effects of sleep disturbance, depression, and fatigue on functional performance may be augmented through multiple interactions.[120] Better understanding of the relationships between these symptoms could help clinicians target therapies for more efficient and effective overall symptom control. Although no single model of these relationships has been consistently supported, the largest study to date, by Stepanski et. al. (2009) modeled the relationship between five commonly clustered symptoms (depression, pain, disturbed sleep, fatigue, and drowsiness), and found sleep to influence both pain and fatigue.[81]

In the general population, sleep disturbance is associated with widespread detrimental effects. Sleep loss can disrupt the immune system, leading to increased inflammatory activity and decreased immune cell response,[44-47] and has also been linked to metabolic changes, including impaired glucose tolerance, up-regulated appetite, and decreased energy expenditure.[43] Chronic sleep disruption is a risk factor for a wide range of illnesses, including anxiety and depression,[52-55] alcohol abuse,[56] hypertension,[57] stroke,[58] diabetes,[59] obesity,[59,60] In light of this, it is likely that sleep disturbance may interact with more cancer symptoms than those with which it is most commonly associated.

1.2.4 Treatments for sleep disturbance

Treatments for sleep disturbance include pharmacologic and non-pharmacologic interventions. Among non-pharmacological approaches, cognitive behavioral therapy for insomnia (CBT-I) is the most studied in the setting of cancer; it is free of adverse effects and it appears to be efficacious.[121-124] CBT-I works by correcting beliefs and behaviors that interfere with sleep, and, while the therapeutic effects are long-lasting, they are slow to manifest.[3] Therefore, CBT-I may be ineffectual for patients needing acute relief or whose insomnia is not primarily due to beliefs and behaviors. Immediate effects, on the other hand, can be achieved with sleep-promoting medications (*hypnotics*) such as benzodiazepines (BZDs; flurazepam, temazepam, triazolam), benzodiazepine receptor agonists (BzRAs; zolpidem, eszopiclone, zaleplon) and melatonin agonists (ramelteon).[125-130 125,128-131] Certain antidepressants (doxepin, trazodone, mirtazapine),[125-127] anticonvulsants (gabapentin, pregabalin),[132-134] and antipsychotic (olanzapine, quetiapine) [125-127] medications also have sleep promoting effects, as do many antihistamines (diphenhydramine, doxylamine, chlorpheniramine, promethazine, hydroxyzine).[125-127]

1.2.5 Evidence relating to treatment of sleep disturbance in cancer

1.2.5.1 Prevalence of hypnotic use

Hypnotic use appears to be common in oncology [**Table 1.1**]. In a 2004 survey of 1,984 Canadian patients, 41% received prescriptions for hypnotics, 37% had used hypnotics at some time since their diagnosis, and 23% were currently using hypnotics.[135] Predictors of hypnotic use included anxiety or psychological difficulties, chemotherapy (current or past), opioid use, and older age.[135] The vast majority (79%) used BZDs, followed by antidepressants (10%), and zopiclone (9%).[135] These results are consistent with an earlier (1996) study of 1,012 Canadian patients with cancer, in which 22% reported hypnotic use (hypnotic type was not specified).[89] Hypnotic use was especially high in patients with lung cancer (40%), and lowest for those with genitourinary cancers (15%).[89] Similarly, in a study of 909 oncology patients in Israel in the late 1990s, 25.7% reported using sleeping pills or tranquilizers in the previous week.[136] Higher rates of hypnotic use were observed in a study of 100 outpatients with terminal cancer in Western Canada; more than half (53%) reported using some intervention for sleep disturbance, with sleep medication (unspecified) being the most common (37%).[82]

Studies on the use of hypnotics in US oncology patients date back to the 1970s, but recent data are lacking. In 1977, Derogatis et. al.[137] surveyed 1,579 inpatients at five large cancer centers in the northeast and California over a six-month period. The mean age was 54 years, 52% had recurrence of a primary lesion, and 58% had metastatic disease. The majority of subjects were female (60%), white (80%), and married (66%). In this sample, 38% were prescribed hypnotics (barbiturates, chloral derivatives, and benzodiazepines) and hypnotics accounted for 48% of all prescribed psychotropics.[137] The authors noted, however, that the estimate may have been inflated by routine use of hypnotics for surgical patients. Sleep was indicated as the prescribing reason for 85% of hypnotics and 44% of all psychotropics (including anxiolytics, antidepressants, and anticonvulsants).[137] The most frequently prescribed hypnotic was the benzodiazepine flurazepam (71%), followed by the barbiturate pentobarbital (19%), and chloral derivatives (9%).[137]

In the 1980s, hypnotic use remained high, but the choice of hypnotic class changed markedly. As evidenced in the following studies, barbiturates and chloral derivatives were replaced with the relatively safer benzodiazepine and antihistamine hypnotics.

Between January 1981 and February 1982, Jaeger et. al.[138] surveyed 1,000 patients with advanced cancer at Cavalry Hospital, New York. Mean age was 68.2 years, and 93% of subjects had metastatic disease.[138] Females made up 55% of the sample, the racial distribution was 73% white, 23% black, and 4% other, and marital status was: 34% married, 37% widowed, 17% single, 13% divorced.[138] More than half (56%) of participants were prescribed a hypnotic (diphenhydramine, flurazepam, or pentobarbital) and hypnotics comprised 33% of psychotropic (anxiolytics, antidepressants, hypnotic) prescriptions.[138] Sleep was the prescribing reason for 94% of hypnotic prescriptions and 34% of all psychotropic prescriptions.[138] The most frequently prescribed hypnotic was the antihistamine diphenhydramine (66%), followed by the benzodiazepine flurazepam (32%), and the barbiturate pentobarbital (2%).[138]

Table 1.1 Estimates of hypnotic us in persons with cancer.

Study Authors	Study Period	Sample Size	Hypnotic Users	Hypnotic Types	Sample Population
Outside the United States					
Paltiel et. al. [136]	Apr 1997–Nov 1998	909	26%	Not specified	Oncology patients in three Israeli hospitals
Casault et. al.[135]	2004	1,984	22%	Not specified	Patients visiting the outpatient oncology clinic at the L'Hôtel-Dieu de Québec in Canada
Sela, Watanabe, & Nekolaichuk[82]	Published in 2004	100	37%	Not specified	Outpatients with terminal cancer in Western Canada
Inside the United States, prior to the introduction of benzodiazepine receptor agonists (current standard of care)					
Derogatis et. al.[137]	Apr 1977 – Sep 1977	1,579	38%	71% Flurazepam[a] 19% Barbiturate pentobarbital 9% Chloral derivatives	Inpatients at five large cancer centers in the northeast United States and California
Jaeger et. al.[138]	Jan 1981 – Feb 1982	1,000	56%	66% Diphenhydramine[b] 32% Flurazepam[a] 9% Barbiturate pentobarbital	Patients with advanced cancer at Cavalry Hospital, New York
Stiefel et. al.[139]	Dec 1987	200	43%	42% Diphenhydramine[b] 33% Triazolam[a] 8% Midazolam[a] 6% Chloral derivatives 5% Pentobarbital 3% Phenobarbital 3% Temazepam[b]	Charts of 200 consecutive adult patients admitted to Memorial Sloan-Kettering Cancer Center, New York
Inside the United States, after to the introduction of benzodiazepine receptor agonists (current standard of care)					
Guo et. al.[140]	Sep 2002 – Oct 2003	96	24%	Not specified	Acute rehabilitation inpatients at M.D. Anderson Cancer Center, Houston, Texas
Koopman et. al.[141]	Published in 2002	97	37%	Not specified	Women with metastatic or locally recurrent breast cancer
Costantini, Ale-Ali, and Helsten[142]	April 1, 2008 to March 31, 2010	124	32%	39% Benzodiazepines 37% Benzodiazepine receptor agonists 9% Trazodone[c] 6% Gabapentin[d] 6% Melatonin 2% Diphenhydramine[b] + acetaminophen	Women receiving chemotherapy for breast cancer

[a] Benzodiazepine, [b] Antihistamine, [c] Antidepressant, [d] Anticonvulsant

In 1987, Stiefel et. al. reviewed medical charts of 200 patients admitted to the Memorial Sloan-Kettering Cancer Center, New York.[139] Just over half (55%) were male, and mean age was 52 years. Mean time since diagnosis was 23 months, and the majority (86%) had a history of (or current) metastatic disease.[139] Almost half (43%) of psychotropic prescriptions were for hypnotics (benzodiazepines, barbiturates, chloral derivatives, and diphenhydramine), and hypnotics comprised 95% of all prescriptions for sleep.[139] The most frequently prescribed hypnotics were benzodiazepines (44%), followed by the antihistamine diphenhydramine (41%), barbiturates (9%), and chloral derivatives (6%).[139]

In 1992, zolpidem (Ambien®, Sanofi) became the first benzodiazepine receptor agonist (BzRA) to enter the US market, followed by zaleplon (Sonata®, Pfizer) in 1999 and eszopiclone (Lunesta®, Sunovion Pharmaceuticals) in 2004.[143] With the hypnotic efficacy similar to benzodiazepines, but fewer side effects, BzRAs (also called Z-meds) quickly became the drug of choice for sleep disturbance. In 2003, benzodiazepines represented only about 11% of prescriptions for insomnia in the US, while antidepressants and BzRAs accounted for about 22% and 18%, respectively.[144] Since 2000, hypnotic use in the general population has increased overall, but BzRA use has grown most dramatically, increasing nearly four-fold from 2000 to 2010.[145] BzRAs are now the most commonly prescribed medication for insomnia in the US (about 38% of prescriptions), followed closely by the antidepressants trazodone and doxepin (36%, combined).[145]

Despite the dramatic shift in prescribing patterns for hypnotics in the US population, there is little recent information on their use in oncology. To characterize symptom burden and pharmacologic management of patients with cancer, Guo et. al. reviewed medical records of 96 inpatients with mixed cancer types undergoing acute inpatient rehabilitation between September 1, 2002 and October 31, 2003 at M.D. Anderson Cancer Center, Houston, Texas.[140] Median age was 64 years, and males comprised 53% of the sample.[140] Upon discharge, 24% were given hypnotics (particular drugs or drug classes were not identified).[140]

Two studies have estimated hypnotic use in women with breast cancer. The first, published in 2002 by Koopman et. al., surveyed 97 women with metastatic or locally recurrent breast cancer who were participating in a randomized clinical trial of psychotherapy for psychosocial adjustment.[141] Mean age was 53.0 years, and the racial distribution was 90% white, 6% Asian, 1% black, 1% Native American, and 2% other.[141] Just over half (53%) were married, 35% were separated, divorced, or widowed, and 1% had never been married.[141] About one-third (37%) of this sample reported use of sleeping pills (unspecified) within the last 30 days, with higher frequency of use among those also reporting pain or depressive symptoms.[141]

From April 1, 2008 to March 31, 2010, Costantini, Ale-Ali, and Helsten evaluated sleep aid prescribing practices for 124 women receiving chemotherapy for breast cancer. Mean age was 51 years, 57.3% were premenopausal, and 62.1% were married. Sleep aid use prior to chemotherapy was reported by 13.7% of patients, and 32.3% received prescriptions for sleep aids during chemotherapy. The most commonly prescribed sleep aids were benzodiazepines (39.2%), followed by BzRAs (37.2%), the antidepressant trazodone (9.8%), the anticonvulsant gabapentin (5.9%), melatonin (5.9%), and the antihistamine diphenhydramine (with acetaminophen, 2%).[142]

Beyond these studies, little is known about current patterns of hypnotic use in the US in persons with cancer. Given the prevalence of sleep disturbance and historical patterns of hypnotic use in these patients, it is reasonable to expect that hypnotic use remains high. It is, therefore, important to characterize patterns of use, as such information is essential for evaluation of healthcare distribution, utilization, and outcomes.

1.2.5.2 Outcomes associated with hypnotic use in persons with cancer

Despite a history of frequent hypnotic use in oncology, there is scant evidence, to date, regarding their use in this population.

Benzodiazepines for treatment of sleep disturbance have been evaluated in two studies of patients with terminal cancer, and one study of women undergoing surgery for breast cancer. Ehsanullah et. al. (1982) randomly assigned 24 patients with terminal cancer to one of two treatment groups: 5 mg diazepam or 10 mg diazepam.[146] After five nights, and a two-day drug free washout period, subjects were switched to the other dose for an additional 5 nights.[146] Seven patients died before completing the study.[146] Each morning, nurses rated subjects as sleeping “well”, “the same”, or “badly” the previous night.[146] Most patients were rated as having slept well at both the 5 mg dose (15/19) and 10 mg dose (17/21), but side effects were common, especially daytime drowsiness (58%), dry mouth (29%), and amnesia (21%).[146]

Matsuo and Morita retrospectively reviewed use of midazolam (n=104, mean dose=10 mg) and flunitrazepam (n=59, mean dose=2 mg) in patients with terminal cancer who were treated in Japan between April 2002 through July 2005.[147] Efficacy was rated as “poor”, “fair”, or “good” based on subjective reports by patients and/or clinicians, as recorded in medical records.[147] Presence of adverse events (hangover, delirium, and/or respiratory depression) was evaluated in a similar fashion.[147] Efficacy was 91% for midazolam (63% good, 28% fair) and 81% for flutrazepam (44% good, 37% fair), and as with the previous study, adverse events were common for both midazolam and flutrazepam: hangover (34% and 19%, respectively), next morning delirium (11% and 15%), and respiratory depression (3.8% and 17%).[147]

In a double-blinded, placebo-controlled trial published in 1994 by Jacobsen et. al., 100 women who had received 0.125 mg of triazolam the night before surgery for breast cancer were randomized to triazolam 0.125 mg (n = 49, with the option to increase to 0.25 mg on subsequent nights) or placebo (n = 51) for three nights.[148] Seventy-nine participants completed all three nights of the study, 84% of the triazolam group (n = 41) and 75% of the placebo group (n = 38).[148] For patients who withdrew after night two (N = 15, triazolam n = 6, placebo n = 9), data for night two were substituted for night three.[148] No participant was removed from the study due to poor response or adverse reactions, but eleven participants chose to discontinue (triazolam n = 4, placebo n = 7).[148] Each morning, subjects were asked to estimate the time to sleep onset (minutes) and number of wakings after sleep onset, and to evaluate general quality of sleep (1 = very bad, to 7 = very good).[148] In addition, two visual analog scales (VAS, 100mm) were used to estimate difficulty falling asleep (0 = easiest ever, to 100 = hardest ever) and feeling rested the following morning (0 = not al all rested, to 100 = as rested as I have ever been).[148] Compared to the placebo group, patients on triazolam had less difficulty falling asleep ($p = 0.002$), reported fewer awakenings ($p = 0.004$), felt more rested in the morning ($p = 0.008$), and rated their sleep quality higher ($p < 0.001$).[148] There was no difference in estimated time to fall asleep.[148]

Two BzRAs, zolpidem and eszopiclone, have been studied in patients with cancer. Joffe et. al. investigated whether adding zolpidem to venlafaxine could improve sleep for women experiencing menopausal symptoms from breast cancer treatment.[149] This double-blinded study randomized 53 women to zolpidem 10 mg (n = 25) or placebo (n = 28) for five weeks between February 2004 and July 2007.[149] Thirty-eight women completed the study, 88% on zolpidem and 57% on placebo.[149] Improved sleep was defined as a decrease in wake time after sleep onset (WASO) of at least 15 minutes (measured objectively by actigraphy) or a decrease (improvement) of at least 3 points on the Pittsburgh Sleep Quality Index (a subjective measure).[149] More women in the zolpidem group had improved sleep (40% vs 14%; $p = 0.035$), and endpoint scores in the zolpidem group improved (WASO improved 9%, PSQI score improved 15%), whereas scores worsened in the placebo group (WASO worsened 2%, PSQI worsened 26%).[149]

Between September 2006 and December 2009, eszopiclone was evaluated in patients with hematologic malignancies who experienced mucositis pain severe enough to require patient-controlled analgesia (PCA).[150] PCA provides a continuous infusion of intravenous opioid analgesia, and also allows patients to self-administer, within limits, additional boluses of medication as needed. Dimsdale et. al. randomized 45 patients to eszopiclone (n = 22, 2-3 mg, depending on age and potential drug interactions) or placebo (n = 23) for two nights.[150] Sleep measures (time to fall asleep, time asleep, number of wakings, depth of sleep, level of sleepiness) were based on patients' subjective reports, surveyed each morning.[150] Likert-type scales were used for both depth of sleep (0 = poor, to 10 = excellent) and level of sleepiness (0 = very sleepy, to 10 = not sleepy at all).[150] The eszopiclone group reported greater total sleep time (mean difference = 84.07 min, $p = 0.05$), fewer number of wakings (mean difference = -2.82, $p < 0.001$), better sleep quality (mean difference = 2.09, $p = 0.05$), and better sleep depth (mean difference = 1.57, $p =$

0.05).[150] Time to fall asleep and current level of sleepiness were not significantly different, and there were no significant differences in use of opioid analgesia.[150]

Some medications used “off-label” for sleep disturbance (see Section 2.4.2) have also been evaluated in persons with cancer. Kim et. al. (published in 2008) conducted a four-week open-label trial of mirtazapine for treatment of nausea, vomiting, and insomnia in Korean patients with cancer and depression.[151] Of the forty-two subjects originally enrolled, seventeen (41%) completed the four-week study.[151] Four patients discontinued due to side effects: sedation (2), constipation (1), and weakness (1).[151] Patients evaluated their sleep using 5-point Likert scales for: ease of sleep, quality of sleep, ease of waking in the morning, and ability to function after waking.[151] Improvements to ease of sleep, quality of sleep, and ability to function were reported as early as day one, while ease of waking improved at day five.[151] In addition, scores for depression improved from the first week, and, for subjects experiencing nausea and vomiting from chemotherapy, symptoms improved from the first day of mirtazapine administration.[151]

Trazodone was studied in 30 patients with insomnia who were receiving palliative care for advanced cancer at Osaka University Hospital between December 2008 and November 2011.[152] Tanimuki et. al. administered a starting dose of 12.5 – 25 mg, and increased to 25 – 50 mg until insomnia improved.[152] Fifteen patients (50%) achieved improved sleep within seven days without requesting a dose increase.[152] In addition, of four subjects from the original sample who reported experiencing troublesome nightmares, two reported improvements after initiation of trazodone.[152]

Between March 2007 and March 2009, Chen et. al. conducted a randomized, placebo-controlled trial to evaluate melatonin for improvement of mood, sleep, and hot flashes in survivors of breast cancer.[153] Ninety-five women were randomized to melatonin (3 mg, n = 48) or placebo (n = 47) for four months, and 52% of those subjects reported poor sleep in the month preceding enrollment (56% on melatonin, 43% on placebo).[153] Eighty-six (91%) participants completed the study; four from the melatonin group withdrew due to side effects (headaches, insomnia, nightmares).[153] Sleep was evaluated at baseline and at four months with the Pittsburgh Sleep Quality Index (PSQI), which subjectively measures sleep quality, latency, duration, efficiency, and disturbances, as well as hypnotic use and daytime dysfunction during the last month.[153] In the melatonin group, average overall PSQI score was 1.67 points lower (better), compared to placebo (95% CI 0.67–2.66, p = 0.001), and mean changes in PSQI total score were -1.9 and -0.1, respectively ($p < 0.001$).[153] No differences were observed for depression or hot flashes.[153]

Finally, Palesh et. al. studied the effects of paroxetine on sleep problems in patients receiving chemotherapy between June 1997 and April 1999.[154] Paroxetine is a serotonin-selective reuptake inhibitor (SSRI) antidepressant, and is not commonly used for sleep, as it lacks the sedative effects of less selective antidepressants (insomnia is, in fact, a common side effect).[155] Nonetheless, Palesh et. al. found promising results. After a second cycle of chemotherapy, 426 subjects were randomized to a 60-day supply of paroxetine 20 mg (n = 217) or placebo (n = 209).[154] Sleep was assessed with three questions that asked participants to quantify the number of nights they had trouble with: falling asleep, waking in the middle of the night, or waking up too early.[154] Fewer patients in the paroxetine group reported sleep problems (79%) compared to patients on placebo (88%, $p < 0.05$), but overall prevalence of sleep disturbance remained high.[154]

These appear to be the only studies to evaluate outcomes associated with hypnotic use in persons with cancer, and the paucity of evidence is reflected in published recommendations and guidelines for the management of sleep disturbance in this population.

1.2.5.3 Guidelines for hypnotic use in persons with cancer

The National Comprehensive Cancer Network (NCCN), Multinational Association of Supportive Care in Cancer (MASCC), European Society For Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) have developed supportive care guidelines for several cancer symptoms, including pain, fatigue, nausea and vomiting, mucositis, and distress. To date, however, only the Oncology Nursing Society (ONS) and the Canadian Partnership Against Cancer have published guidelines on the management of sleep disturbance. The recommendations of both groups are substantially limited by inconsistent evidence in support of

CBT-I interventions and a paucity of experimental data supporting the use of hypnotics.[156,157] In addition to these guidelines, there have been several published reviews of evidence relating to treatment of insomnia in cancer. Two of these, Langford et. al. (2012)[158] and Dickerson et. al. (2014)[111] reviewed only nonpharmacological interventions and will not be discussed further in this section.

In 2002, Hirst and Sloan published a Cochrane review on the use of benzodiazepines and BzRAs in palliative care.[159] The initial sample of 404 potential studies was reduced to 37 on the basis of relevance.[159] This selection was further reduced to three studies for issues relating to study design and/or level of detail.[159] Ultimately, the remaining three studies were excluded due to lack of usable data, and the authors were unable to make any recommendations.[159]

Since 2002, several publications have reviewed evidence related to management of sleep disturbance in persons with cancer. Most conclude that there is sufficient evidence to support the use of cognitive behavioral therapies, but evidence related to pharmacological treatment of sleep disturbance appears in only a few publications and most offer little or no guidance on the use of medications for sleep disturbance in persons with cancer.

In a review for the Oncology Nursing Society, Page et. al. (2006) found, "no published meta-analysis or experimental design study," examining the efficacy of hypnotics in patients with cancer, and assigned hypnotics to the category, "Benefits Balanced with Harms," indicating that clinicians and patients should evaluate risks and benefits on a case by case basis.[156] In a follow-up review, Berger (2009) also reported that, "no intervention studies have tested the effects of prescription sleep drugs in patients with cancer," and made no recommendations regarding their use.[160]

A 2007 review by Fiorentino and Ancoli-Israel notes that the National Institutes of Health State of the Science Conference on Insomnia determined BzRAs and ramelteon to be safer than benzodiazepines, and provides details (e.g., dosing, side effects, cost) for those medications. No studies on the effects of hypnotics in patients with cancer are cited, however, and no further recommendations regarding their use are made. [161]

In 2012, Langford, Lee, and Miaskowski published a comprehensive review and meta-analysis of sleep disturbance interventions in oncology. No pharmacological interventions were included.[158]

Also in 2012, Palesh et. al. published a review of sleep disturbance (prevalence, causes, and management) in patients undergoing chemotherapy.[162] The authors reported finding no assessment of sleep aids in persons receiving chemotherapy, and cautioned against the possibility of harmful drug interactions.[162]

A third publication in 2012, by Pachman et. al., reviewed treatments for fatigue, neuropathy, and pain, as well as insomnia, in cancer survivors.[110] This review included the studies on mirtazapine,[151] trazodone,[152] and paroxetine[154] in persons with cancer, but concluded that, overall, there was insufficient evidence to recommend any pharmacologic intervention.[110]

A review of psychopharmacology in oncology by Caruso et. al. published in 2013 cites two investigations of antidepressants for treatment of sleep disturbance, the Tanimukai et. al.[152] study on trazodone and the Palesh et. al.[154] study on paroxetine, both of which had positive, if modest, results.[163] Use of benzodiazepines is discouraged, due to the potential for respiratory depression, and the authors remain equivocal on use of BzRAs, citing lack of evidence.[163]

A Pan-Canadian practice guideline for sleep disturbance in adults with cancer was also published in 2013, by Howell et. al.[164] The guidelines were based upon a systematic review of evidence (published separately, in 2014 by the same authors), which included the small, randomized controlled trial (RCT) of eszopiclone in patients with mucositis pain.[150] The remainder of the review, however, cited data from non-cancer populations because, "no RCT data involving pharmacological interventions for insomnia in cancer were identified."[157] In the guidelines, Howell et. al. advocated for non-pharmacological approaches, such as prevention, supportive education, and cognitive behavioral therapy for insomnia (CBT-I), as first line therapy, and recommended that pharmacotherapy be reserved for augmentation (e.g., while waiting for CBT-I to take effect) or rescue (e.g., for patients too ill to complete CBT-I), and for no more than four weeks.[164] No recommendations regarding specific medications were made, but clinicians were advised to base their selection on patient-specific factors, such as age, primary sleep complaint, and potential for drug interactions.[164]

Also in 2014, Davis and Goforth published a review on the effects of, and interventions for, insomnia in cancer, and, as with the review by Howell et. al., pharmacotherapy trials cited were all conducted in non-cancer populations.[165] Nonetheless, Davis and Goforth concluded, despite the "weak evidence," that clinicians should consider multimodal treatment approaches that include both nonpharmacological and pharmacological interventions, and observed that many medications have additional effects that could provide added benefits for persons with cancer.[165]

Finally, a similar conclusion was made by Scalo and Rascati that same year.[166] After reviewing the therapeutic and adverse effects of sleep disturbance medications, as observed in non-cancer populations, the authors discussed how each therapy might ameliorate (or exacerbate) the unique needs of persons with cancer [**Table 1.2**].[166]

Table 1.2 Potential benefits and risks of commonly used hypnotics for patients with cancer.

Drug Class	Drugs	Potential Benefits	Potential Risks
Benzodiazepines (BZDs)	Estazolam* Flurazepam* Quazepam* Temazepam* Triazolam* Alprazolam Lorazepam Clonazepam	– Anxiolytic – Longer duration than BzRAs	– Significant fall risk – Next day residual effects may worsen CRF – Withdrawal and/or rebound on discontinuation – Risk of respiratory depression when combined with opioid analgesics – REM sleep suppression
Benzodiazepine Receptor Agonists (BzRAs)	Eszopiclone* Zaleplon* Zolpidem*	– Fewer side effects than BDZs – Extended-release, sublingual, and spray formulations are available	– Risk of parasomnias, anterograde amnesia – Dose-dependent next day residual effects – Significant fall risk – Withdrawal syndrome – REM sleep suppression
Melatonin Agonists	Melatonin Ramelteon*	– Excellent safety profile – Better efficacy in older patients – May help to correct circadian rhythms – Possibly antioxidant, antiproliferative – Low fall risk	– None documented
Tricyclic Antidepressants	Doxepin*	– Low fall risk – May improve neuropathic pain – Antidepressant (at higher doses)	– Risk of cardiac conduction abnormalities – Risk of anticholinergic effects – Risk of SIADH, hyponatremia
Other Sedating Antidepressants	Mirtazapine	– Low fall risk – Preserves sleep architecture – Improved appetite and weight gain – Minimal risk of anticholinergic effects, cardiotoxicity, SIADH, hyponatremia – Effective for depression at low doses – Anxiolytic & antiemetic – May improve neuropathic pain	– May cause or exacerbate restless leg syndrome or periodic limb movements
	Trazodone	– Anxiolytic, antidepressant (high doses) – May improve neuropathic pain	– Risk of SIADH, hyponatremia – Risk of cardiac conduction abnormalities
Sedating Antipsychotics	Olanzapine Quetiapine	– Effective for delirium (Recommended for short-term use only)	– Risk of metabolic syndrome, neuroleptic malignant syndrome, and blood dyscrasias – Risk of SIADH, hyponatremia
Anticonvulsants	Gabapentin Pregabalin	– May improve neuropathic pain	– Peripheral edema may exacerbate CHF – Rare cases of blood dyscrasias, hyponatremia
Antihistamines	Diphen-hydramine† Doxylamine† By Rx only: Hydroxyzine Promethazine	– Antiemetic – Anxiolytic	– Strongly anticholinergic - may exacerbate CRF and/or opioid-induced constipation – Tolerance can develop with continued use – Residual sedation may exacerbate CRF Promethazine: – Risk of cardiotoxicity, neuroleptic malignant syndrome, bone marrow suppression

CHF: congestive heart failure, CRF: cancer-related fatigue; REM: rapid eye movement, Rx: prescription, SIADH: syndrome of inappropriate diuretic hormone

* Prescription medication with FDA approval for treatment of insomnia

† Non-prescription medication with FDA approval for use as a night-time sleep aid

1.3 SECTION III: RATIONALE FOR PROPOSED STUDY

Sleep disturbance warrants special consideration in patients with cancer. In addition to the usual risk factors, oncology patients encounter numerous other sleep disruptors, and the incidence of sleep disturbance is high in this setting. Sleep disturbances also have more severe consequences for persons with cancer, including exacerbation of other symptoms, diminished quality of life, and worsened prognoses. Effective treatment of sleep disturbances is, therefore, an essential component of supportive care.

There is some evidence that nonpharmacologic therapies, which correct beliefs and behaviors that interfere with sleep, are effective in persons with cancer. Such therapies may not be appropriate, however, for patients with limited time or functional status or for those whose sleep disturbance has other causes. Pharmacologic interventions, on the other hand, can offer rapid relief, and some may offer therapeutic benefits for other symptoms, such as depression, anxiety, or anorexia. There is little known, however, about the safety and efficacy of hypnotic drugs in persons with cancer.

The first rationale for this research is to delineate more clearly the use of hypnotics in persons with cancer. Several US studies have measured hypnotic use in oncology prior to the 1990s. The introduction of benzodiazepine receptor antagonists in the late 20th century, however, has dramatically altered prescribing practices in the general US population,[145] and it is unclear whether this extends to the oncology setting. From the few studies conducted so far, hypnotic use appears to be common, with estimates hovering near 30%.[82,140-142] Even less is known about the distribution of hypnotic use by drug class, but results from one study indicate a relatively high reliance on benzodiazepines (39.2% of all hypnotics prescribed).[142] Given the potential for adverse events, especially in persons with cancer, it is important to obtain current data on how commonly benzodiazepines, as well as other hypnotics, are prescribed. The proposed study of hypnotic use will have the largest and most diverse population to date (> 2,700 patients from 38 regionally dispersed sites), which will improve generalizability. In addition, the data set includes an abundance of variables describing patient characteristics and outcomes, which will allow patterns of hypnotic use in sub-samples to be described as well.

The second rationale is the need for more data on outcomes associated with hypnotic use in oncology. Despite the prevalence of sleep disturbance and hypnotic use in persons with cancer, there is, to date, little guidance on the pharmacologic management of sleep disturbance in this population. Recommendations are substantially limited by the paucity of experimental data.[156,157] The proposed study will contribute to the literature as a comprehensive exploration of symptom burden and quality of life outcomes associated with hypnotic use in patients with cancer. The data available for analysis will allow comparisons of outcomes between subjects using and not using hypnotics, with outcomes variables that are scaled in intensity. Although the retrospective design of this study will limit what conclusions can be drawn, the findings may reveal drug–outcome relationships that should be further explored in prospective trials.

Finally, this study is motivated by the need to better understand relationships between sleep and other symptoms. Many cancer symptoms occur concomitantly and interactions between them have been observed.[90,167,168] Understanding how these symptoms influence each other is key to optimizing symptom management. Cancer-related pain, fatigue, and depression have commonly been associated with sleep disturbance, but given the multifarious somatic effects of sleep, it is reasonable to hypothesize that relationships exist between sleep and other cancer symptoms that are less frequently measured (e.g., cognitive function, appetite loss).[169] Studies testing this hypothesis may help to uncover important causal pathways to target therapeutically.

Chapter 2: Methodology

CHAPTER OVERVIEW

This chapter documents the methodology that was used to evaluate hypnotic use and associated outcomes in persons with cancer, beginning with a listing of the specific aims and hypotheses. The general study design is outlined, followed by detailed descriptions of the data source and study variables, the analysis plans for each specific aim, and the sample size requirements for each analysis. A discussion of study limitations closes the chapter.

2.1 SECTION I: SPECIFIC AIMS

For a population of patients with cancer, the aims of this study are:

1. To quantify the prevalence of reported sleep disturbances and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to sleep disturbance.

2. To quantify the prevalence of hypnotic use and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to hypnotic use.

3. To quantify reported change in sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to change in sleep disturbance.

4. To evaluate whether or not symptom burden and health-related quality of life outcomes differ on the basis of sleep disturbance or hypnotic use, controlling for demographic, disease, and treatment characteristics.

2.2 SECTION II: HYPOTHESES

2.2.1 Specific Aim 1

To quantify the prevalence of <u>sleep disturbance</u> and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to sleep disturbance in the study cohort.

H_0 (1a): Demographic characteristics (age, sex, race, employment status, driver status, history of depression) will not differ significantly when cohort is ranked by severity of reported sleep disturbance.

H_0 (1b): Disease characteristics (cancer site, cancer stage, age at diagnosis, time since diagnosis, progression status, performance status, weight loss) will not differ significantly when cohort is ranked by severity of reported sleep disturbance.

H_0 (1c): Treatment characteristics (current chemotherapy, current radiotherapy, clinician type, opioid analgesia, clinician assessments of symptom burden and quality of life, difficulty to treat, medication use for symptom management) will not differ significantly when cohort is ranked by severity of reported sleep disturbance.

H_0 (1d): Symptom burden (pain, fatigue, nausea, vomiting, distress, shortness of breath, cognitive difficulty, anorexia/cachexia, drowsiness, dry mouth, depression, numbness/tingling, diarrhea, constipation, sore mouth, rash/itching, hair loss, cough) will not differ significantly when cohort is ranked by severity of reported sleep disturbance.

H_0 (1e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not related to level of reported sleep disturbance [scale: 0 = “not present” to 10 = “as bad as you can imagine”].

2.2.2 Specific Aim 2

To quantify the prevalence of <u>hypnotic use</u> and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to hypnotic use in the study cohort.

H_0 (2a): Demographic characteristics (age, sex, race, employment status, driver status, history of depression) will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.

H_0 (2b): Disease characteristics (cancer site, cancer stage, age at diagnosis, time since diagnosis, progression status, performance status, weight loss) will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.

H_0 (2c): Treatment characteristics (current chemotherapy, current radiotherapy, clinician type, opioid analgesia, clinician assessments of symptom burden and quality of life, difficulty to treat, medication use for symptom management) will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.

H_0 (2d): Symptom burden (pain, fatigue, nausea, vomiting, distress, shortness of breath, cognitive difficulty, anorexia/cachexia, drowsiness, dry mouth, depression, numbness/tingling, diarrhea, constipation, sore mouth, rash/itching, hair loss, cough) will not differ significantly will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.

H_0 (2e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not related to use of hypnotics or the use of a specific class of hypnotic.

2.2.3 Specific Aim 3

To quantify change in sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are associated with change in sleep disturbance in the study cohort.

H_0 (3a): Demographic characteristics (age, sex, race, employment status, driver status, history of depression) will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.

H_0 (3b): Disease characteristics (cancer site, cancer stage, age at diagnosis, time since diagnosis, progression status, performance status, weight loss) will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.

H_0 (3c): Treatment characteristics (current chemotherapy, current radiotherapy, clinician type, opioid analgesia, clinician assessments of symptom burden and quality of life, difficulty to treat, medication use for symptom management) will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.

H_0 (3d): Symptom burden (pain, fatigue, nausea, vomiting, distress, shortness of breath, cognitive difficulty, anorexia/cachexia, drowsiness, dry mouth, depression, numbness/tingling, diarrhea, constipation, sore mouth, rash/itching, hair loss, cough) will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.

H_0 (3e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not associated with change in level of reported sleep disturbance.

2.2.4 Specific Aim 4

To evaluate whether or not symptom burden and health-related quality of life outcomes differ on the basis of sleep disturbance or hypnotic use, controlling for demographic, disease, and treatment characteristics.

H_0 (4a): Symptom burden outcomes (pain, fatigue, nausea, being distressed, dyspnea, cognitive difficulties, anorexia/cachexia, drowsiness, dry mouth, sad/depressed, vomiting, numbness/tingling, diarrhea, constipation, sore mouth, rash/pruritus, hair loss, coughing) will not differ significantly on the basis of level of reported sleep disturbance.

H_0 (4b): Quality of life outcomes (based on six domains: general activity, mood, work, relations with other people, walking, and enjoyment of life) will not differ significantly on the basis of level of reported sleep disturbance.

H_0 (4c): Symptom burden outcomes (pain, fatigue, nausea, being distressed, dyspnea, cognitive difficulties, anorexia/cachexia, drowsiness, dry mouth, sad/depressed, vomiting, numbness/tingling, diarrhea, constipation, sore mouth, rash/pruritus, hair loss, coughing) will not differ significantly on the basis of level of reported hypnotic use.

H_0 (4d): Quality of life outcomes (based on six domains: general activity, mood, work, relations with other people, walking, and enjoyment of life) will not differ significantly on the basis of level of reported hypnotic use.

Table 2.1 Hypotheses for Specific Aim 1

Hypothesis	DV	Level	IV	Level	Statistical Test
Specific Aim 1: To quantify the prevalence of sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to sleep disturbance in the study cohort.					
H_0 (1a): Demographic characteristics will not differ significantly when cohort is ranked by severity of reported sleep disturbance.	Ranked sleep disturbance severity score	Continuous	Age Sex Race Employment status Driver status History of depression	Categorical Binary Categorical Categorical Binary Binary	Welch's ANOVA
H_0 (1b): Disease characteristics will not differ significantly when cohort is ranked by severity of reported sleep disturbance.	Ranked sleep disturbance severity score	Continuous	Cancer site Cancer stage Age at diagnosis Time since diagnosis Progression status Performance status Weight loss	Categorical Categorical Categorical Categorical Categorical Categorical Categorical	Welch's ANOVA
H_0 (1c): Treatment characteristics will not differ significantly when cohort is ranked by severity of reported sleep disturbance.	Ranked sleep disturbance severity score	Continuous	Current chemotherapy Current radiotherapy Clinician type Opioid analgesia Clinician assessments of symptom burden and quality of life Difficulty to treat Medication use for symptom management	Binary Binary Categorical Binary Ordinal Ordinal Categorical	Welch's ANOVA
H_0 (1d): Symptom burden will not differ significantly when cohort is ranked by severity of reported sleep disturbance.	Ranked sleep disturbance severity score	Continuous	Pain Fatigue Nausea Vomiting Distress Shortness of breath Cognitive difficulty Anorexia/cachexia Drowsiness Dry mouth Depression Numbness/tingling Diarrhea Constipation Sore mouth Rash/itching Hair loss Cough	Ordinal / Continuous	Welch's ANOVA
H_0 (1e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not related to the level of reported sleep disturbance [scale: 0 = "not present" to 10 = "as bad as you can imagine"].	Sleep disturbance severity score	Continuous	Multiple, from dependent variables above	Mixed: may be continuous, ordinal, categorical, or binary	Linear regression

Table 2.2 Hypotheses for Specific Aim 2

Hypothesis	IV	Level	DV	Level	Statistical Test
Specific Aim 2: To quantify the prevalence of hypnotic use and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to hypnotic use in the study cohort.					
H_0 (2a): Demographic characteristics will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.	Hypnotic use (yes/no)	Binary	Age Sex Race Employment status Driver status History of depression	Categorical Binary Categorical Categorical Binary Binary	Pearson chi-square
H_0 (2b): Disease characteristics will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.	Hypnotic use (yes/no)	Binary	Cancer site Cancer stage Age at diagnosis Time since diagnosis Progression status Performance status Weight loss	Categorical Categorical Categorical Categorical Categorical Categorical Categorical	Pearson chi-square
H_0 (2c): Treatment characteristics will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.	Hypnotic use (yes/no)	Binary	Current chemotherapy Current radiotherapy Clinician type Opioid analgesia Clinician assessments of symptom burden and quality of life Difficulty to treat Medication use for symptom management	Binary Binary Categorical Binary Ordinal Ordinal Categorical	Pearson chi-square
H_0 (2d): Symptom burden will not differ significantly when cohort is dichotomized as users/nonusers of hypnotics or categorized by type of hypnotic used.	Hypnotic use (yes/no)	Binary	Pain Fatigue Nausea Vomiting Distress Shortness of breath Cognitive difficulty Anorexia/cachexia Drowsiness Dry mouth Depression Numbness/tingling Diarrhea Constipation Sore mouth Rash/itching Hair loss Cough	Ordinal / Continuous	Pearson chi-square
H_0 (2e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not related to the use of hypnotics or the use of a specific class of hypnotic.	Hypnotic use (yes/no)	Binary	Multiple, from dependent variables above	Mixed: may be continuous, ordinal, categorical, or binary	Logistic regression

Table 2.3 Hypotheses for Specific Aim 3

Hypothesis	IV	Level	DV	Level	Statistical Test
Specific Aim 3: To quantify change in sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to change in sleep disturbance in the study cohort.					
H_0 (3a): Demographic characteristics will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.	Sleep disturbance change group	Continuous	Age Sex Race Employment status Driver status History of depression	Categorical Binary Categorical Categorical Binary Binary	Welch's ANOVA
H_0 (3b): Disease characteristics will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.	Sleep disturbance change group	Continuous	Cancer site Cancer stage Age at diagnosis Time since diagnosis Progression status Performance status Weight loss	Categorical Categorical Categorical Categorical Categorical Categorical Categorical	Welch's ANOVA
H_0 (3c): Treatment characteristics will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.	Sleep disturbance change group	Continuous	Current chemotherapy Current radiotherapy Clinician type Opioid analgesia Clinician assessments of symptom burden and quality of life Difficulty to treat Medication use for symptom management	Binary Binary Categorical Binary Ordinal Ordinal Categorical	Welch's ANOVA
H_0 (3d): Symptom burden will not differ significantly when cohort is categorized by change in level of reported sleep disturbance.	Sleep disturbance change group	Continuous	Pain Fatigue Nausea Vomiting Distress Shortness of breath Cognitive difficulty Anorexia/cachexia Drowsiness Dry mouth Depression Numbness/tingling Diarrhea Constipation Sore mouth Rash/itching Hair loss Cough	Ordinal	Welch's ANOVA
H_0 (3e): Demographic characteristics, disease characteristics, treatment characteristics, and symptom burden are not related to change in level of reported sleep disturbance.	Change in sleep disturbance severity score	Continuous	Multiple, from dependent variables above	Mixed: may be continuous, ordinal, categorical, or binary	Linear regression

Table 2.4 Hypotheses for Specific Aim 4

Hypothesis	IV	Level	DV		Level	Statistical Test
Specific Aim 4: To evaluate whether or not symptom burden and quality of life outcomes differ on the basis of sleep disturbance or hypnotic use, controlling for demographic, disease, and treatment characteristics.						
H_0 (4a): Symptom burden outcomes will not differ significantly on the basis of level of reported sleep disturbance [scale: 0 = "not present" to 10 = "as bad as you can imagine"].	Change in sleep disturbance score	Continuous	Pain Fatigue Nausea Vomiting Distress Shortness of breath Cognitive difficulty Anorexia/cachexia Drowsiness	Dry mouth Depression Numbness/tingling Diarrhea Constipation Sore mouth Rash/itching Hair loss Cough	Continuous	Linear regression
H_0 (4b): Quality of life outcomes will not differ significantly on the basis of level of reported sleep disturbance [scale: 0 = "not present" to 10 = "as bad as you can imagine"].	Change in sleep disturbance score	Continuous	General activity Mood Work (including around the house) Relations with other people Walking Enjoyment of life		Continuous	Linear regression
H_0 (4c): Symptom burden outcomes will not differ significantly on the basis of the use of hypnotics or the use of a specific class of hypnotic.	Hypnotic use/non-use	Binary	Pain Fatigue Nausea Vomiting Distress Shortness of breath Cognitive difficulty Anorexia/cachexia Drowsiness	Depression Numbness/tingling Diarrhea Constipation Sore mouth Rash/itching Hair loss Cough	Continuous	Hotelling's T^2, corrected for heteroscedasticity
H_0 (4d): Quality of life outcomes will not differ significantly on the basis of the use of hypnotics or the use of a specific class of hypnotic.	Hypnotic use/non-use	Binary	General activity Mood Work (including around the house) Relations with other people Walking Enjoyment of life		Continuous	Hotelling's T^2, corrected for heteroscedasticity

2.3 Section III: Institutional Review Board Approval

The Institutional Review Board (IRB) of The University of Texas at Austin (Federalwide Assurance #2030) has determined that this study does not meet the criteria for human subjects research as defined in the Common Rule (45 CFR 46) or FDA Regulations (21 CFR 56), and, therefore, does not require IRB oversight. Specifically, IRB review and oversight is not required because the study activities involve secondary use of a de-identified data set that has no direct identifiers or links to identifiers.

2.4 Section IV: Study Design

The study was a secondary analysis of data from the Symptom Outcomes and Practice Patterns (SOAPP) study (ECOG E2Z02, NCT00303914), a prospective observational study with a primary objective of gathering reliable data on how cancer symptoms affect patients and how those symptoms are treated.[170] The SOAPP study took place over two clinic visits, approximately four weeks apart, during which patients and clinicians were surveyed. The patient survey included assessments of nineteen cancer-related symptoms and six items measuring the extent to which symptoms interfered with health-related quality of life.

Specific Aims 1 and 2 were cross-sectional evaluations of the prevalence and correlates of sleep disturbance and hypnotic use, respectively. Specific Aim 3 evaluated correlates of longitudinal change in sleep disturbance. Specific Aim 4 evaluated longitudinal change in symptom burden and quality of life outcome measures associated with sleep disturbance and hypnotic use.

2.5 Section V: Data Source

Data for the study were originally collected during the Symptom Outcomes and Practice Patterns (SOAPP) study (ECOG E2Z02, NCT00303914) conducted by the

Eastern Cooperative Oncology Group (ECOG).[170] ECOG, one of the largest clinical cancer research organizations, is a collaboration of public and private clinics and research institutes in the United States and abroad. The study was chaired by Michael J. Fisch, MD, MPH, Chair of the Department of General Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, and by Charles S. Cleeland, PhD, McCullough Professor of Cancer Research, Department of Symptom Research, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center.[170] Permission to use the SOAPP data has been generously granted by Dr. Fisch and his collaborators, including Judith Manola and Fengmin Zhao, who were instrumental in providing the data.

2.5.1 Study population and data collection

The SOAPP study was conducted at multiple, randomly selected sites that agreed to participate.[170] From March 3, 2006 to May 19, 2008, the SOAPP study enrolled adult patients receiving care for lung, breast, prostate, or colorectal cancer at academic centers and community oncology clinics in Illinois, Indiana, Iowa, Michigan, and South Dakota.[170] To reduce selection bias, each site devised a system for recruiting participants.[170] Of the 38 participating sites, 13 had at least 40 percent minority participation.[171]

Patients were recruited for the SOAPP study upon checking in for a scheduled appointment, and those that agreed to participate completed baseline symptom assessment surveys prior to meeting with their clinician.[170] Demographic and clinical information was also collected from patients at this time.[170]

After the visit, clinicians provided additional clinical information, and were also surveyed on their evaluation of the patient's symptom burden and quality of life.[170] Symptom surveys were repeated, for both patients and clinicians, at a follow-up visit four to five weeks later.[170]

Table 2.5 Overview of cohort characteristics – SOAPP study respondents with sleep disturbance scores (N = 2,748)

Characteristic	**Mean**	**SD**
Age	61.16	12.3
Age at diagnosis	58.20	12.3

Characteristic	**N**	**%**
Sex		
Female	1926	70.1
Male	822	29.9
Race		
White	2349	86.5
Black	314	11.6
Other	52	1.9
	Missing = 33	
Ethnicity		
Non-Hispanic	2273	89.7
Hispanic	251	9.9
Refused	11	0.4
	Missing = 213	
Primary Disease Site		
Breast	1367	49.8
Colorectal	647	23.5
Lung	449	16.3
Prostate	285	10.4

SOAPP: Symptom Outcomes and Practice Patterns
SD: standard deviation

Inclusion Criteria: Outpatients who were at least 18 years of age, at any stage of care for invasive breast, lung, prostate, or colorectal cancer, and willing to take the follow-up survey were eligible to participate in the SOAPP study.[171,172]

Exclusion Criteria: Patients with inadequate cognitive function, as assessed by a study screener, were excluded from the original SOAPP study.[172] For the present study, subjects missing a score on the sleep disturbance item at either the first or second visit were also excluded.

The final sample size of the SOAPP study was 3,106.[171] After exclusion of subjects with missing sleep disturbance scores, the sample for the present study was 2,748. **Table 2.5** provides an overview of cohort characteristics.

2.5.2 Survey instruments

2.5.2.1 Patient survey

MDASI

The MD Anderson Symptom Inventory (MDASI) is a validated instrument measuring the intensity of 13 cancer symptoms, including disturbed sleep, during the past 24 hours.[173] Development of the MDASI began with an initial list of 26 symptoms and interference items collected from panels of clinicians.[173] Clinical judgment, along with cluster and factor analyses, were used to identify the core items that represented overall symptom burden for patients with cancer.[173] The final 13 core items are: pain, fatigue, nausea, disturbed sleep, distress (upset), shortness of breath, memory problems, lack of appetite, feeling drowsy, dry mouth, feeling sad, vomiting, and numbness or tingling.[173] For each core symptom, there is one item on the MDASI survey.[173] Patients rate each symptom on an 11-point Likert-type scale (0 = "not present" to 10 = "as bad as you can imagine").[173]

The MDASI also includes six items measuring the interference of overall symptom burden with health-related quality of life (HRQoL) items: general activity, mood, work (including around the house), relations with other people, walking, and enjoyment of life.[173] The interference items are measured on a similar 11-point scale (0 = "did not interfere", 10 = "interfered completely").[173]

In initial testing, the thirteen symptoms measured by the MDASI accounted for 64% of the variability in HRQoL interference.[173] Construct validity was tested with principal axis factor analysis, which yielded two factors (general symptoms and gastrointestinal symptoms) onto which the thirteen symptoms loaded.[173] These two factors, along with the HRQoL interference items, were tested for internal consistency in two different samples.[173] Cronbach's alpha values ranged from 0.82 to 0.94, indicating high internal consistency (reliability).[173] To test sensitivity, subjects were dichotomized by severity of disease, as measured by performance status ('good' or 'poor'); differences were observed for both mean symptom severity (2.36 vs. 3.62; $p <$ 0.001) and mean symptom interference (2.95 vs. 5.31; $p < 0.001$).[173] Sensitivity to treatment was examined by comparing patients who had not received cancer treatment in the previous three months against a group undergoing bone marrow transplantation and a group receiving chemotherapy.[173] No difference in overall mean symptom severity was detected, but overall mean symptom interference was greater in the transplant and chemotherapy groups than in the group not currently receiving cancer treatment (5.22 vs. 4.43 vs. 3.23, $p < 0.01$).[173]

In 2014, the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee published a consensus statement recommending a core set of symptoms that should be measured in trials of cancer treatments (in adults).[174] The list was developed through a multi-step process that included systematic literature review, analysis of six large datasets with symptom measures, and multi-stakeholder review by a panel of experts and patient representatives.[174] The MDASI instrument contains all recommended core items except: constipation, and diarrhea. The SOAPP study added those two symptoms, along with four more (sore mouth, hair loss, cough, and rash/itching).

Standard interpretations of the MDASI have yet to be established in the literature, but the authors suggest that a change of about one point can be considered a minimally important (i.e., clinically significant) difference (MID).[175] The rationale for this is that one-half standard deviation has been commonly used as an MID threshold, and, in initial validation studies, the standard deviations for the 13 core symptoms ranged from 1.95 to 2.31.[175] In a systematic review of health-related quality of life studies, Norman, Sloan, and Wyrwich (2003) concluded that, in most cases, the detection threshold for meaningful change was approximately one-half standard deviation.[176] Other authors have argued, however, that no ideal method for determining MID has yet been identified, and, even with a consistent method, results may differ across subpopulations.[177,178] Nonetheless, for the purposes of the present study, the suggested MID of one point will be used.

Interpretation of symptom severity using MDASI scores is also not fully defined, to date. Based on instruments previously developed by the MDASI authors, cut points have been established for pain and fatigue. The pain[179] and fatigue[180] instruments were scaled the same way as the MDASI (0 = "none" to 10 = "as bad as you can imagine"), and optimal cut points for both were 1 – 4 for mild, 5 – 6 for moderate, and 7 – 10 for severe.[179,181] Although prior findings are not conclusive, cut-points of 5 and 7 are also often associated with clinically meaningful differences for other 0 to 10 scales used for symptom assessment in oncology (e.g., Edmonton Symptom Assessment Scale, the Brief Fatigue Inventory, and the Brief Pain Inventory).[179,180,182] Therefore, this study used the same cut points, checked against histograms.

Appendix A contains a copy of the patient survey.

2.5.2.2 Clinician survey

Clinician Survey

After indicating what type of clinician is completing the survey (attending physician, resident or fellow, advanced practice nurse or nurse practitioner, physician assistant, or other), the clinicians were asked to provide clinical information about the patient, including: cancer site, cancer stage, age at diagnosis, time since diagnosis, performance status, and whether the patient is undergoing radiotherapy or chemotherapy. Then, mirroring the patient's non-MDASI items, clinicians were asked to rate (0 to 5) the patient's overall quality of life, and the extent to which the patient is bothered by difficulties relating to: cancer, other diseases, cancer treatments, symptom management medications, and weight change. Finally, clinicians are asked to rate the difficulty of caring for the patient (1="very difficult", 2="difficult", 3="average", 4="easier than average", 5="much easier than average").[170]

Appendix B contains a copy of the clinician survey.

2.5.3 Study variables

2.5.3.1 Dependent variables

Specific Aims 1a, 1b, and 1c, sleep disturbance score (0 = "none" to 10 = "as bad as you can imagine"), was ranked prior to bivariate analysis to correct for a strong zero bias in the distribution. Specific Aim 1d used the original sleep disturbance severity score as a continuous variable. Non-parametric models (including Poisson, zero-inflated Poisson, ordinal logistic, and zero-inflated beta) were initially evaluated, but linear regression analysis, treating sleep disturbance severity score as a continuous variable, produced the best-fitting models.

For Specific Aim 2, subjects were dichotomized on the basis of hypnotic use (yes / no); sample size did not permit categorization by hypnotic class. In the original SOAPP study, clinicians identified patient medication use by category. The 'hypnotics' category was subdivided into benzodiazepines (BZDs), and non-BZDs. Examples listed for non-BZD hypnotics were zolpidem (a BZD receptor agonist) and chloral hydrate. Chloral hydrate is not commonly used in recent studies of the general population nor in oncology studies dating just before the introduction of BZD receptor agoninsts (BzRAs). Therefore, this study assumed 'non-benzodiazepine hypnotics' to represent mainly BzRAs. BZDs were further partitioned into long- / intermediate-acting (e.g, clonazepam, clorazepate, flurazepam, lorazepam) and short-acting (e.g., oxazepam, triazolam, alprazolam) because short-acting BZDs are sometimes used for anxiety, independently of sleep disturbance. Categorization by duration of action is not consistent in the literature, however, and SOAPP clinicians may have assigned BZDs differently.

Table 2.6 Definitions of dependent variables

Dependent Variables	Level	Definition
Specific Aim1: To quantify the prevalence of sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to sleep disturbance in the study cohort.		
Sleep disturbance score	Continuous	0: Not present –to– 10: As bad as you can imagine
Specific Aim 2: To quantify the prevalence of hypnotic use and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are related to hypnotic use in the study cohort.		
Hypnotic use	Binary	0: No 1: Yes
Specific Aim 3: To quantify change in sleep disturbance and evaluate whether or not demographic characteristics, disease characteristics, treatment characteristics, symptom burden, or medication use are associated with change in sleep disturbance in the study cohort.		
Change in sleep disturbance severity	Continuous	Visit 2 score – visit 1 score Range: -10 to +10
Specific Aim 4: To evaluate whether or not symptom burden and quality of life outcomes differ on the basis of sleep disturbance or hypnotic use.		
Change in severity of: pain, fatigue, nausea, being distressed, dyspnea, cognitive difficulties, anorexia/cachexia, drowsiness, dry mouth, sad/depressed, vomiting, numbness/tingling, diarrhea, constipation, sore mouth, rash/pruritus, hair loss, coughing	Continuous	Visit 2 score – visit 1 score Range: -10 to +10
Change in interference with: general activity, mood, work, relations with other people, walking, and enjoyment of life	Continuous	Visit 2 score – visit 1 score Range: -10 to +10

Specific Aims 3a, 3b, 3c, and 3d, evaluated change in sleep disturbance severity score from the first to second visit (range: -10 to + 10). For bivariate analyses, change in sleep disturbance score was binned into

Dependent variables for Specific Aims 4a and 4c, were the changes in symptom severity scores from the first to second visit (range: -10 to + 10). Specific Aims 4b and 4d evaluated changes in symptom interference scores for the six health-related quality of life items from the first to second visit (range: -10 to + 10).

Definitions of classification variables can be found in **Table 2.6**.

2.5.3.2 Proposed correlates of sleep disturbance and hypnotic use

Variables that were evaluated as correlates of sleep disturbance and hypnotic use are defined in **Table 2.7**. Selection of variables was based, in part, on the '3P' model of insomnia, which characterizes risk factors as predisposing, precipitating, and/or perpetuating.* Predisposing factors for insomnia include physiological, psychological, or social circumstances that increase one's vulnerability to sleep disruption; precipitating factors are life events that trigger acute insomnia; and perpetuating factors inhibit one's ability to adapt and resume normal sleeping patterns.[183] The SOAPP study measured numerous variables, allowing for broad exploration of potential sleep disturbance correlates. Interpretation is limited, however, by lack of information pertaining to timing. For example, initiation of treatment (e.g., chemotherapy, corticosteroids) may precipitate sleep disturbance, while continued treatment may perpetuate sleep disturbance. Because timing data (initiation and duration) are mostly unavailable in this study, distinctions between precipitation and perpetuation cannot be made, nor can causality be inferred. Therefore, factors will be treated as correlates only.

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* The terms *sleep disturbance* and *insomnia* are often used interchangeably. It should be noted, however, that the term *sleep disturbance* may encompass a wider range of complaints (e.g., restless leg syndrome, obstructive sleep apnea).

Demographic variables are: age, sex, race, employment status, driver status, and history of depression [**Table 2.7.a**]. Disease characteristics are: cancer site, cancer stage, age at diagnosis, time since diagnosis, progression status, performance status, and weight loss [**Table 2.7.b**]. Treatment characteristics are: current chemotherapy, current radiotherapy, clinician type, opioid analgesia, clinician assessments of symptom burden and quality of life, clinician assessment of difficulty to treat, and medications used for symptom management [**Table 2.7.c**]. Among medications used to manage cancer symptoms, this study included those known or suspected to have effects on sleep: long-, mid-, and short-acting benzodiazepines, benzodiazepine receptor agonists, steroids, tricyclic antidepressants, antiepileptics for pain, antidepressants for pain, phenergan, neurokinin-1 inhibitors, reglan, and 5-ht3 antagonists [**Table 2.7.d**]. Symptom burden variables are: pain, fatigue, nausea, vomiting, distress, shortness of breath, cognitive difficulty, anorexia/cachexia, drowsiness, dry mouth, depression, numbness/tingling, diarrhea, constipation, sore mouth, rash/itching, hair loss, and cough [**Table 2.7.e**].

Table 2.7 Definitions of correlate variables

Table 2.7.a Demographic characteristics

Variable	Level	Definition
Age	Continuous	Age at registration
Sex	Binary	1: Male 2: Female
Race	Categorical	1: White 2: Black 3: Others
Ethnicity	Categorical	1: Hispanic 2: Non-Hispanic 10: Patient refusal 11: Site refusal
Employment status	Categorical	1: Working Full-Time 2: Working Part-Time 3: Not in workforce (e.g., retired, disabled, student, homemaker)
Employment change	Binary	1: No 2: Yes
Drive within the past 4 weeks	Binary	1: No 2: Yes
Personal history of depression	Binary	1: No 2: Yes
Family history of depression	Binary	1: No 2: Yes

Table 2.7.b Disease characteristics

Variable	Level	Definition
Disease characteristics		
Independent Variable	Level	Definition
Disease site	Categorical	1: Breast 2: Colorectal 3: Prostate 4: Lung
Current stage of disease	Categorical	1: No evidence of disease 2: Local/regional 3: Metastatic 4: Local/regional and met
Diagnosis age	Continuous	Age at first diagnosis of cancer
Diagnosis months	Continuous	Months since cancer diagnosis at registration
Current status of disease	Categorical	1: Complete Disappearance of Lesions 2: Partial Response 3: Stable 4: Progression
ECOG performance status	Categorical or Ordinal	0: Fully active, all pre-disease ability without restriction 1: Restricted in physically strenuous activity but ambulatory 2: Ambulatory and capable of all self care but unable to carry out any work activities 3: Capable of only limited self care, confined to bed or chair more than 50% of waking hours 4: Completely disabled
Weight loss in previous 6 months	Categorical or Ordinal	1: <5% of body weight 2: 5 to <10% of body weight 3: 10 to <20% of body weight 4: ≥20% of body weight

Table 2.7.c Treatment characteristics

Variable	Level	Definition
Current chemotherapy	Binary	1: No 2: Yes
Current radiation therapy	Binary	1: No 2: Yes
Type of clinician		1: Attending Physician 2: Resident or fellow 3: Advanced practice nurse or nurse practitioner 4: Physician assistant 5: Other
Systemic opioids for treating pain	Binary	1: No 2: Yes
Support group	Binary	1: No 2: Yes
Counseling	Binary	1: No 2: Yes
Clinician assessments of patient's level of difficulty relating to: – Comorbidity – Cancer – Cancer treatment – Symptom management medications – Weight change	Ordinal	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Clinician assessment of patient's overall quality of life	Ordinal	1: Very poor 2: Poor 3: Fair 4: Good 5: Excellent
Clinician assessment of difficulty in caring for patient	Ordinal	1: Very difficult 2: Difficult 3: Average 4: Easier than average 5: Much easier than average

Table 2.7.d Medications used for symptom management

Variable	Level	Definition
Long-acting benzodiazepines	Binary	0: No 1: Yes
Mid-acting benzodiazepines		
Short-acting benzodiazepines		
Benzodiazepine receptor agonists		
Steroids		
Tricyclic antidepressants		
Antiepileptics for pain		
Antidepressants for pain		
Phenergan		
Neurokinin-1 inhibitors		
Reglan		
5-HT3 antagonists		

Table 2.7.e Cancer symptoms other than disturbed sleep

Independent Variable	Level	Definition
Pain	Ordinal or Continuous	0: Not present –to– 10: As bad as you can imagine
Fatigue		
Nausea		
Disturbed sleep		
Being distressed		
Dyspnea		
Cognitive difficulties		
Anorexia/cachexia		
Drowsiness		
Dry mouth		
Sad/depressed		
Vomiting		
Numbness/tingling		
Diarrhea		
Constipation		
Sore mouth		
Rash/pruritus		
Hair loss		
Coughing		

2.6 SECTION VI: ANALYSIS PLAN

Statistical analyses were conducted using the following software: Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.), SAS (SAS Institute. 2015. The SAS system for Windows. Release 9.4. SAS Institute, Cary, NC.), Excel (Microsoft®. 2015. Excel for Mac. Version 15), IVEware (University of Michigan. 2002. IVEware: Imputation and Variance Estimation Software), and the Stata module PSMATCH2 (version 4.0.11, 2014).[184]

All regression analyses and statistical tests for significant difference were two-tailed, with an alpha (α, acceptable probability of type I error) of 0.01.

In biomedical research, an alpha of 0.05 is the general standard; that is, a 5 percent chance of a statistical test falsely finding a significant difference is generally considered acceptable. When multiple tests are conducted on a sample, however, the probability of type I error from each study accumulates, resulting in an increased error rate of $1 - (1 - \alpha)^n$ for the study as a whole (where n = the number of statistical tests performed).[185] For example, if ten tests are performed with an alpha of 0.05, then the probability of type I error for all ten tests (i.e., the family-wise error rate) is 40 percent. One way to reduce the family-wise error rate is to assign a smaller alpha to the individual tests. For example, ten tests with an alpha of 0.01 produce a family-wise error rate of ten percent. While this approach reduces the probability of type I error, its cost is an increase in the probability of type II error. That is, as the chance of an overall family-wise false positive result decreases, so does the power of each individual test to detect a true difference.

When interpreting statistical results, the family-wise error rate can be more meaningful than the results of individual tests. For example, when testing the "universal null" hypothesis that groups are identical in all variables, or when performing the same test repeatedly in subsamples (e.g., batches of manufactured items) for the purpose of rejecting or retaining the subsample.[186] It has been argued, however, that in epidemiological and biomedical studies it does not always make sense to interpret multiple endpoints with a "family" level of significance. Adjusting the alpha level can bias studies with multiple endpoints. For example, a clinical trial may miss a true treatment effect if the corresponding statistical test is interpreted with an alpha that was reduced to account for testing the entire family of primary and secondary endpoints.[186] Furthermore, the multiple endpoints of a given study are often chosen arbitrarily and do not necessarily constitute a "family" that should be interpreted using a combined measure of error.[187]

Nonetheless, in the present study, alpha was set to 0.01 based on the following considerations. The proposed study includes a large number of variables, many of which will be tested multiple times. Many of the MDASI symptom burden and quality of life items are intercorrelated, and may conceivably represent families of repeated measures on each subject.[188] Finally, the large sample size provided by the SOAPP study should ensure sufficient power, even with a reduced alpha.

2.6.1 Missing data

Preliminary analysis of the data revealed the low proportions (< 5%) of missing values for most independent variables, except current immunotherapy (49.2%). With a large number of variables, however, list-wise deletion would reduce the sample by about 25%. To preserve the sample, missing data was estimated using multiple imputation.

Imputation is the process of replacing missing values with reasonable estimates. The motivations for imputation are to preserve the sample and to maximize the validity of statistical analyses. If cases with missing values are simply dropped from statistical analyses, the attrition can reduce power and limit the generalizability of results. In addition, analysis of only complete cases can introduce selection bias if groups with missing data differ from those with complete data.[189] Filling in missing data can also introduce bias, however, and carries the risk of underestimating uncertainty and increasing Type I error.[190] For example, a simple approach to imputation is to replace all missing values of a variable with the mean of the existing values. The resulting sample will be biased toward the 'non-missing' mean value, which may not reflect the original sample population. To reduce this bias, a regression model conditioned on other variables can be used to produce different values for different individuals. Although this approach reduces inflation of a single value, a remaining concern is the increased probability of Type I error because the predicted values do not take into account uncertainty in the predictive model. Combining point estimates from multiple imputed datasets (using "Rubin's rules")[191] introduces variability, which, in turn, accounts for some degree of uncertainty related to estimating the missing values.[192]

Mechanisms that cause missing data are classified as: missing at random (MAR), missing completely at random (MCAR), and missing not at random (MNAR).[192,193] For data that are MCAR, the mechanism for missingness has no relationship with any observable variable. This could be the result of, for example, wind scattering and blowing away random sheets from a collection of surveys that were dropped on the ground. Imputation is generally not needed for MCAR data, as list-wise deletion will not bias results, but loss of power may be a concern. Data are MNAR if the reason for missingness is unknown or related to the variables itself. For example, respondents with a particular disease may be unwilling to report it on a survey. In this case, list-wise deletion would bias the sample, and imputation would require an *a priori* model to represent the mechanism for missingness. In MAR data, missingness of a value is related to an observable variable or variables, other than the variable itself. In this case, the related variables can be used to predict the missing value, assuming those variables are represented in the dataset.

Little (1998) proposed a chi-square test for MCAR.[194] Subjects are dichotomized as either having no missing values or at least one missing value, and these groups are then assessed for differences in key variables. Data are assumed to be MCAR if the *p*-value for Little's test is not significant ($p > 0.05$). The SOAPP data failed Little's test ($X^2 = 32.07$, df = 18, $p = 0.022$) with the following variables: sleep score at first visit, hypnotic use at first visit, age group, sex, race, ethnicity, cancer site, months since diagnosis, cancer status, and functional status. There is no established test to determine that data are MAR, but it is a reasonable assumption for the SOAPP data, which include a large number of observed variables and a generally low proportion of missing values.[195,196] It is difficult to evaluate whether data are MNAR, rather than MAR, without additional information, but multiple imputation usually produces unbiased estimates with NMAR data.[197]

The number of imputations required depends, in part, on the fraction of missing information, λ. The fraction of missing information represents, for a given estimate based on *m* imputed datasets, the amount of information missing due to missing values. The formula for λ, adapted from Schafer and Olson (1998)[198], is

$$\lambda = \frac{r + {}^{2}/_{(v+3)}}{1 + r}$$

where *r* is the relative increase in variance due to missing data

$$r = \left(1 + \frac{1}{m}\right)\frac{between\ imputation\ variance}{within\ imputation\ variance}$$

and ν is the degrees of freedom

$$\nu = (m-1)\left[1 + \frac{between\ imputaiton\ variance}{\left(1+\frac{1}{m}\right)\ within\ imputation\ variance}\right]^2$$

In the present study, the fraction of missing information was less than 5% for all variables, except *current immunotherapy*, which had 41% missing information.

Early recommendations suggested that the number of imputations needed could be determined by relative efficiency, a comparison of the variance for an estimate based on m imputed datasets relative to the variance based on an infinite number of imputations, as a metric.[199] Relative efficiency is approximated as $RE = (1 + \lambda/m) - 1$, where λ is the fraction of missing information. In many cases, there will be little change after five imputations. For example, if starting with 50% missing information, the relative efficiency for an estimate based on five imputed datasets is 1.049, meaning that standard deviations for m=5 estimates increase 5% over m=∞ estimates. Newer recommendations take statistical power into account, in addition to variance. In a study that tested several multiple imputation models with varying λ and m, Graham, Olchowski, and Gilreath (2007) showed that power to detect small effect sizes decreased markedly with fewer imputations.[200] From these findings, they recommend that for $\lambda < 0.1$, five imputations are needed.

Among the various methods of imputation, one of the more common approaches is to construct regression models that allow missing values to be predicted conditional on the values of other variables. The simplest approach is to assume a joint model, such as multivariate normality, for all variables. In datasets that include a diversity of distributions, however, joint modeling can produce biased estimates.[201] Fully conditional specification (FCS), on the other hand, incorporates a distribution-specific model for each missing variable into the overall multivariate model.[202] This method is also known as multiple imputation by chained equations,[203] and sequential multiple regression imputation.[201]

FCS is useful for imputation of survey data, as it accommodates variables with varied measurement levels (e.g., continuous, categorical, ordinal) and distribution forms (e.g, parametric, non-parametric, Poisson). Imputing values on a variable-by-variable basis from a sequence of multiple regression models matched to the variable type, and conditioned on all other variables, reduces the risk that imputations of one variable may be inconsistent with others. FCS also allows for imposing restrictions and bounds, and accommodates five types of variables: 1) continuous, 2) dichotomous, 3) categorical with three or more categories, 4) counts, and 5) mixed.[203] Mixed variables are defined as continuous variables with a probability mass at zero. Ordinal data are treated as continuous, but with restrictions imposed to limit the range of values imputed and exclude non-integer values.[204]

Using SAS software (SAS Institute. 2015. The SAS system for Windows. Release 9.4. SAS Institute, Cary, NC.) and a callable routine built with IVEWare (University of Michigan. 2002. IVEware: Imputation and Variance Estimation Software), missing values were multiply-imputed (*m=5*) through sequential multiple regression by chained equations to accommodate heterogeneity of variable type and distribution.[201-203] In addition to the planned study variables, auxiliary variables were included in the multiple imputation models, to provide more information for modeling.

Pooling of the results from ANOVA, [205] chi-squared,[191] and regression[191] analyses was performed with Excel (Microsoft®. 2015. Excel for Mac. Version 15) spreadsheets for ANOVA and chi-square results, and the *mi estimate* command in Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) for regression analyses.

Comparison of imputed datasets by analysis of variance (ANOVA) revealed no differences for any variables, except current hormone therapy ($F=5.54$ [1,13903], $p = 0.0186$). Final analyses were, therefore, performed on a singly-imputed dataset, to permit use of additional analytic procedures, including regression diagnostics.

2.6.2 Statistical analyses

2.6.2.1 Specific Aim 1: Correlates of Sleep Disturbance Severity

The sample was subdivided by cancer type and subsample characteristics were evaluated using ANOVA and chi-squared tests. Regression analysis was used to identify correlates of sleep disturbance severity (SDS). Because SDS scores were discrete and their distribution strongly skewed toward zero, non-parametric models (including Poisson, zero-inflated Poisson, ordinal logistic, and zero-inflated beta) were initially evaluated, but linear regression analysis produced the best-fitting models. The final linear regression model was subjected to diagnostic tests for multicollinearity (variance inflation factors < 3.0 for all variables), outliers and highly influential observations (largest Cook's distance = 0.018), normality of residuals (kernel density plot, Appendix C) and homoscedasticity (Breusch-Pagan test, $p<0.001$). The test for homoscedasticity failed; therefore, robust standard errors were computed for improved validity.[206] Saturated models were reduced based on significance level for each correlation coefficient and model fit was evaluated with Bayesian Information Criterion values. After modeling the total sample, cancer site-specific models were evaluated using the same methods.

2.6.2.2 Specific Aim 2: Correlates of Hypnotic Use

The sample was dichotomized by hypnotic use and subsample characteristics were evaluated using chi-squared tests. Starting with a saturated model, binary logistic regression was used to identify correlates of hypnotic use. Models were reduced based on significance level for each correlation coefficient, and model fit was evaluated with Bayesian Information Criterion values. Probability of hypnotic use was estimated for each factor level and standardized to the total group (covariates controlled using weighted averages).[207,208] After modeling the total sample, cancer site-specific models were evaluated using the same methods.

3.6.2.3 Specific Aim 3: Correlates of Change in Sleep Disturbance Severity

Change in sleep disturbance severity (SDS) was calculated as: SDS Change = Visit 2 SDS score – Visit 1 SDS score. Bivariate analyses were performed with Welch's ANOVA. Starting with a saturated model, linear regression was used to identify correlates of change in SDS score. Models were reduced based on significance level for each correlation coefficient. No further analysis was conducted, as there was no model that met statistical significance.

2.6.2.4 Specific Aim 4: Outcomes Associated with Sleep Disturbance and Hypnotic Use

Participants not using hypnotics were matched to hypnotic users on the basis of Mahalanobis distance within calipers of 0.2 standard deviations of a propensity score.[209] Propensity scores, representing the probability of being in the treatment group were estimated with a probit model of baseline characteristics thought to predict treatment.[210] The Mahalanobis metric is a multidimensional measure of distance between two observations.[211] Each estimate can be used alone to select matches, but use of both, first identifying candidates whose propensity scores are within calipers, then selecting from those based on minimal Mahalanobis distance, appears to provide more balanced samples than either method alone.[209] Average outcomes in the hypnotics group were estimated based on the average of differences across matched cases, and conditional variance was estimated using fifty neighbors (~12.5% of the group size) to produce heteroscedasticity-consistent standard errors.[212] Matching was conducted to reduce the effects of selection bias (where covariates can have confounding effects on outcomes),[210] and to reduce Type-I error risk from heteroscedasticity (exacerbated by unequal group sizes).[213]

Changes in symptom severity and HRQoL between hypnotic users and non-users were compared using Hotelling's T^2 test (an omnibus version of the paired t-test[214]), with degrees of freedom corrected for heteroscedasticity.[215] Following a statistically significant multivariate result, individual symptoms were evaluated with post-hoc two-sided t-tests (with Welch's approximation of degrees of freedom for unequal variance). Multivariate regression, controlling for hypnotic use, was conducted to evaluate how change in severity of sleep disturbance related to changes in other cancer symptoms and HRQoL.

2.7 Section VII: Sample Size Requirements

Statistical power is the probability of a study detecting a difference that truly exists. Although it is defined as 1-β, there are four variables that influence power: 1) the probability of type I error (*alpha*, or α); 2) the probability of type II error (beta, or β); 3) the sample size (*n*); and 4) the magnitude of difference or change to be detected (effect size).[216] For all analyses in this study, values for α and β are set to 0.01 and 0.2, respectively. Samples size requirements are summarized in table **2.8**.

2.7.1 Specific Aim 1: Correlates of sleep disturbance

Correlates of sleep disturbance were evaluated using multiple linear regression, with the null hypothesis (H_0) that cancer-related variables are not associated with severity of sleep disturbance. Assuming a small effect size ($f^2 = 0.02$) and a maximum of 25 correlates, a total of 1,551 cases are required (Figure 2.1).

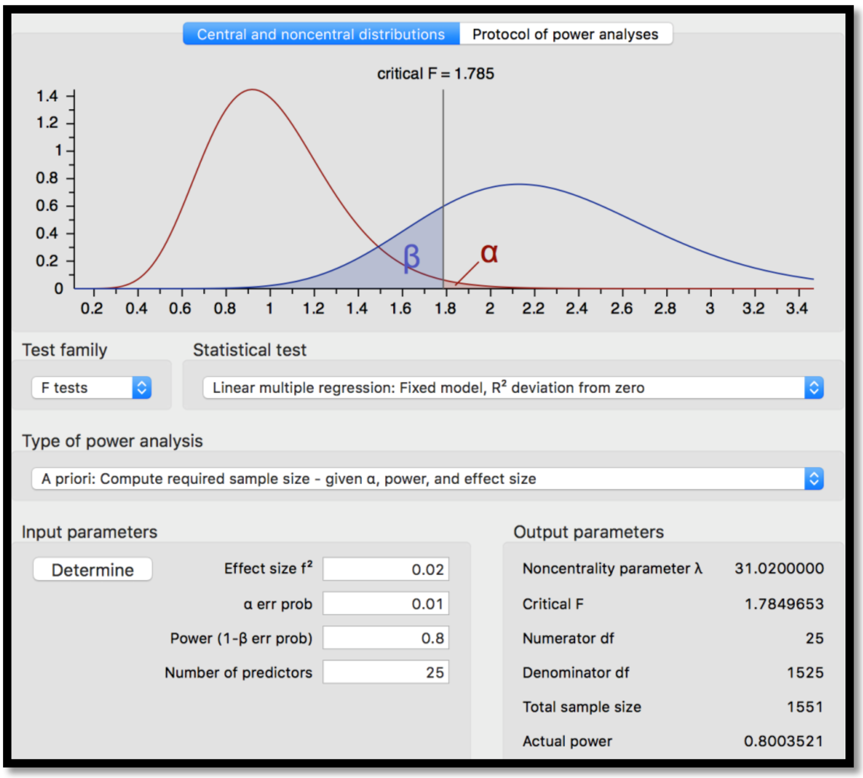

Figure 2.1 G*Power calculation of required sample size for multiple regression with 25 correlates

2.7.2 Specific Aim 2: Correlates of hypnotic use

The effect size for this analysis is the odds ratio of hypnotic use associated with each factor. The odds ratio (OR) for a binary outcome is the ratio of the odds of H_1 (an event X occurring in the presence of factor Y) over the odds of H_0 (event X occurring when factor Y is not present). The formula for OR is

$$OR = \frac{H_1 Pr(Y = 1|X = 1)}{H_0 Pr(Y = 1|X = 0)}$$

For Specific Aim 2, the null hypothesis (H_0) is that cancer-related variables are *not* associated with use of a hypnotic. The event rate for sleep disturbance under the null hypothesis (H_0) was set to five percent. A recent study by Bertisch et. al. estimated that about three percent of Americans use a prescription sleep-aid (including medications used off-label).[145] For persons over sixty years of age, prevalence of hypnotic use ranged from 3.86 percent (ages 60 to 69 years) to 5.26 percent (ages ≥ 80 years).[145]

The alternative hypothesis (H_1) is that cancer-related variables are associated with use of hypnotics. The event rate for the alternative hypothesis was set to twenty percent. Although data for patients with cancer are limited, estimates range from about twenty percent of patients at various stages,[89] to about sixty percent of patients with advanced cancer.[138] The resulting odds ratio is 8.08.

$$OR = \frac{H_1 Pr(Y = 1|X = 1)}{H_0 Pr(Y = 1|X = 0)} = \frac{(0.20/0.80)}{(Y0.03/0.97)} = 8.08$$

To account for correlations among covariates, a large correlation (r = 0.50) was assumed, and R^2 was set to 0.25. To account for all possible variable types, estimations of total sample size required were carried out using G*Power and assuming a normal distribution for X (Total N = 100), an exponential distribution of X (Total N = 56), and a binary distribution of X (Total N = 258), as shown in Figures 2.2.a, b, and c, respectively.

Alternatively,[217] estimating a maximum of twenty-five covariates, and considering intercorrelations among variables and unequal distribution of variables, the required sample size to have fifty cases per variable would be 1,250.

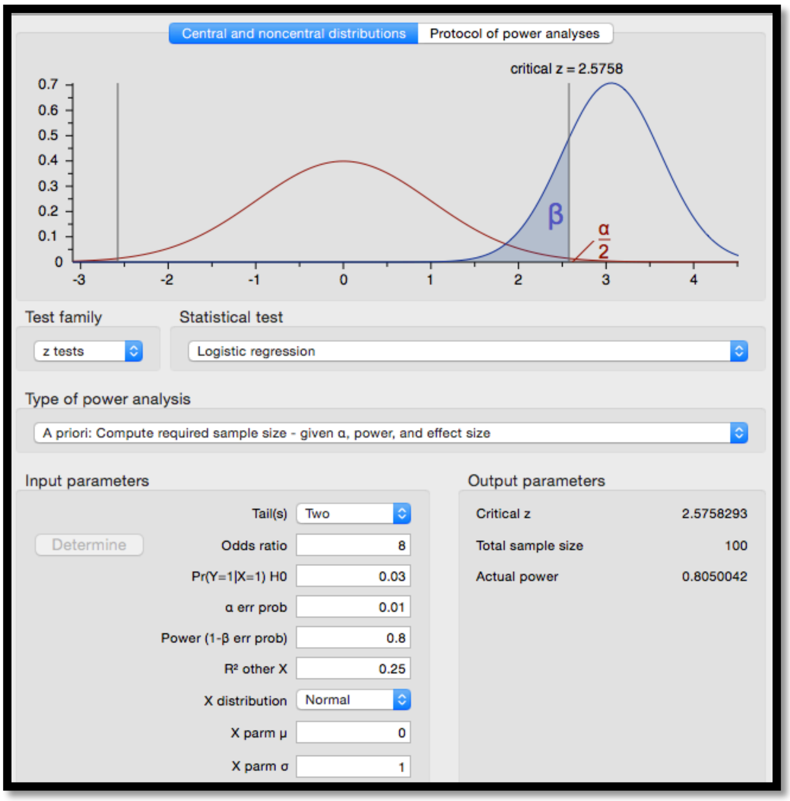

Figure 2.2.a
G*Power calculation of required sample size for logistic regression where X follows a normal distribution

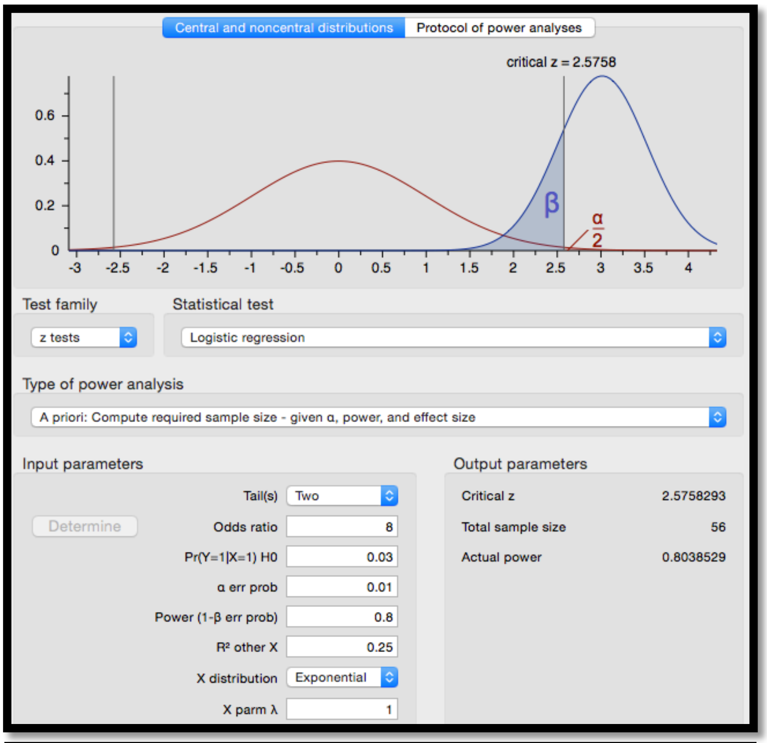

Figure 2.2.b G*Power calculation of required sample size for logistic regression where X follows an exponential distribution

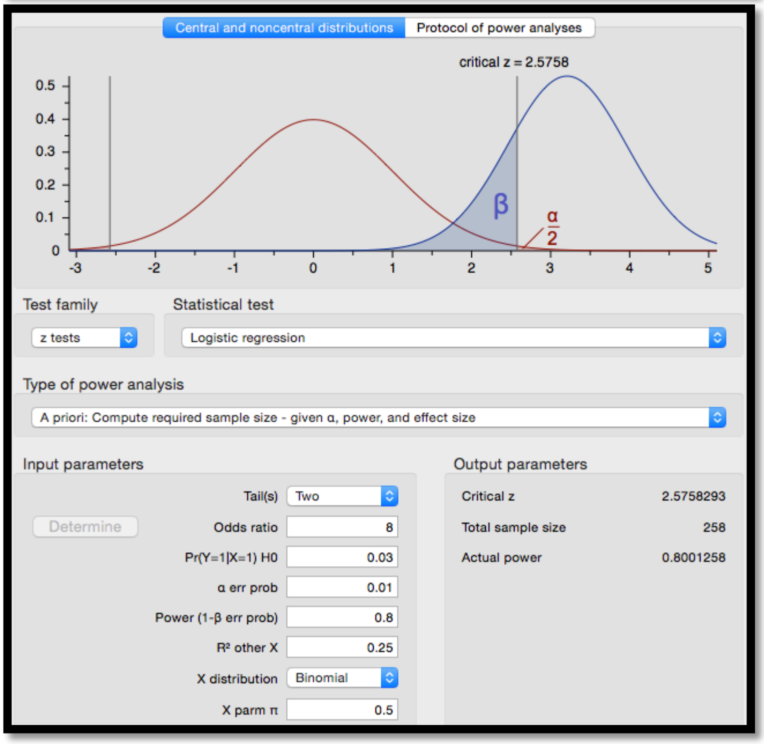

Figure 2.2.c G*Power calculation of required sample size for logistic regression where X follows a binomial distribution

2.7.3 Specific Aim 3: Correlates of change in sleep disturbance

Correlates of change in sleep disturbance were evaluated using multiple linear regression, with the null hypothesis (H_0) that cancer-related variables are not associated with change in sleep disturbance. Assuming a small effect size (f^2 = 0.02) and a maximum of twenty-five covariates, a total of 1,551 cases are required (Figure 2.3).

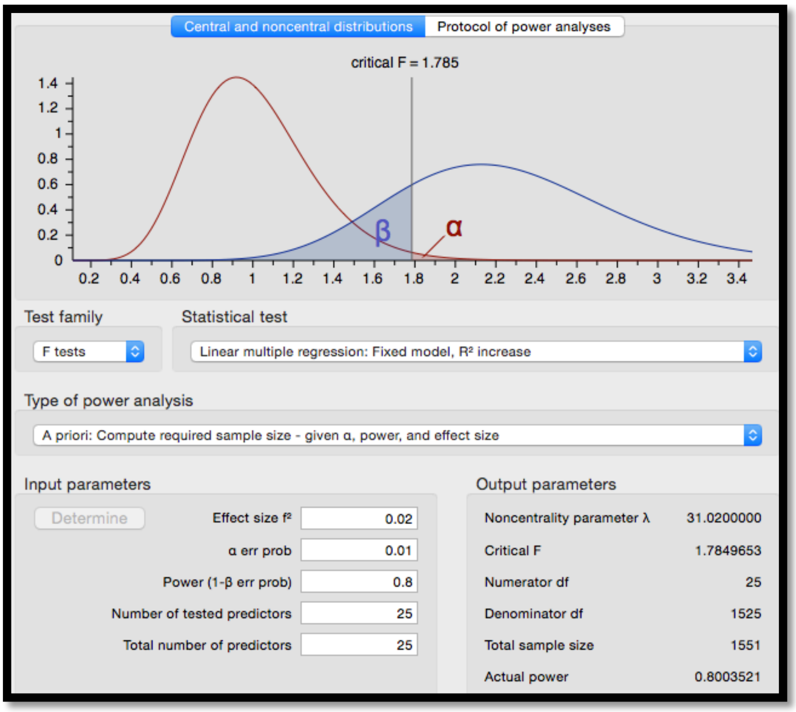

Figure 2.3 G*Power calculation of required sample size for multiple regression with 25 correlates

2.7.4 Specific Aim 4: Outcomes associated with sleep disturbance and hypnotic use

Multivariate linear regression was used to assess associations between changes in sleep disturbance severity and changes in severity of other cancer symptoms. Assuming a small effect size (f^2 = 0.02) and a maximum of eighteen response variables, a total of 1,374 cases are required (Figure 2.4.a).

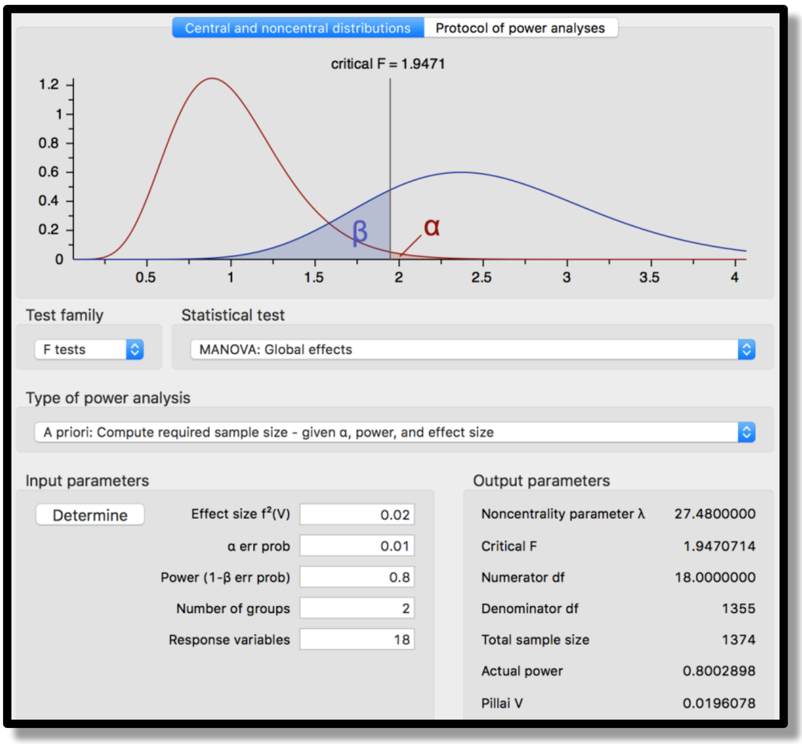

Figure 2.4.a
G*Power calculation of required sample size for multivariate F test with eighteen dependent variables

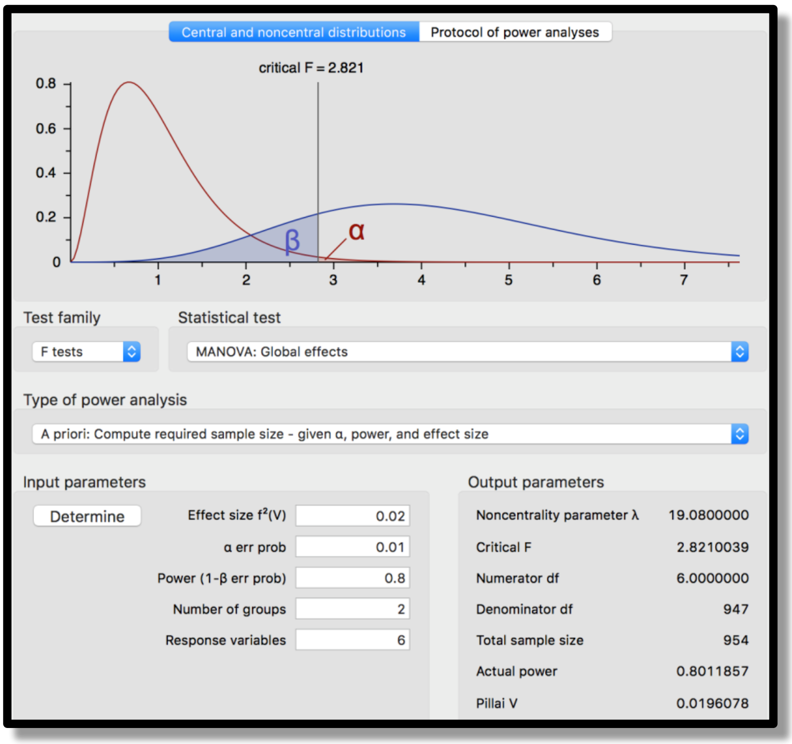

Figure 2.4.b
G*Power calculation of required sample size for multivariate F test with six dependent variables

Multivariate linear regression was also used to evaluate associations between changes in sleep disturbance severity and changes in the degree to which symptom burden interfered with health-related quality of life. Assuming a small effect size (f^2 = 0.02) and a maximum of six response variables, a total of 954 cases are required (Figure 2.4.b).

Hotelling's T^2 test was used to assess associations between hypnotic use and changes in severity of cancer symptoms other than sleep disturbance. Assuming a small effect size (mean change = 0.25) and a maximum of eighteen response variables, each group requires 877 cases (Figure 2.4.c).

Hotelling's T^2 test was also used to evaluate associations between hypnotic use and changes in the degree to which symptom burden interfered with health-related quality of life. Assuming a small effect size (f^2 = 0.02) and a maximum of six response variables, each group requires 609 cases (Figure 2.4.d).

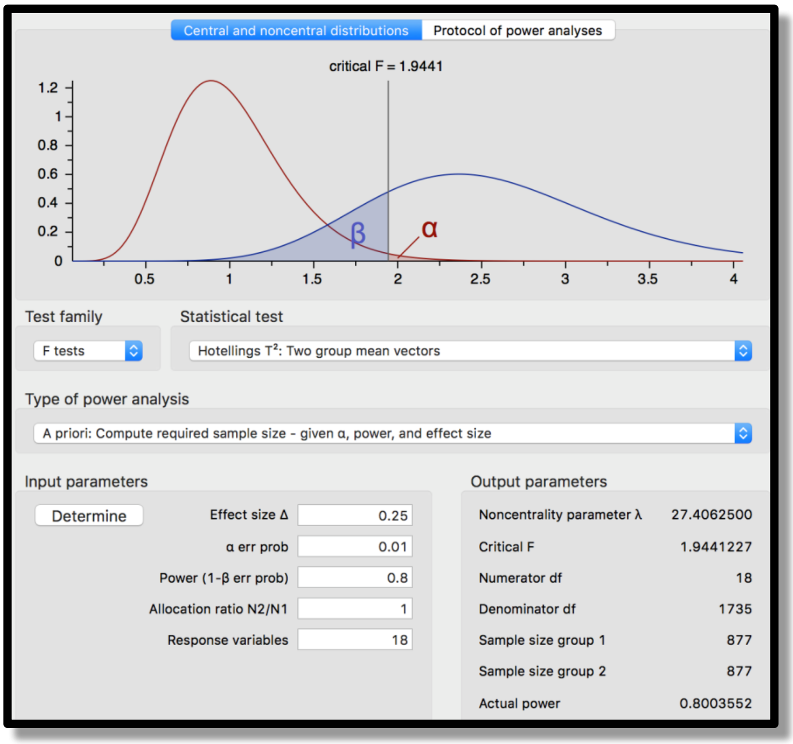

Figure 2.4.c G*Power calculation of required sample size for Hotelling's T^2 test with eighteen dependent variables

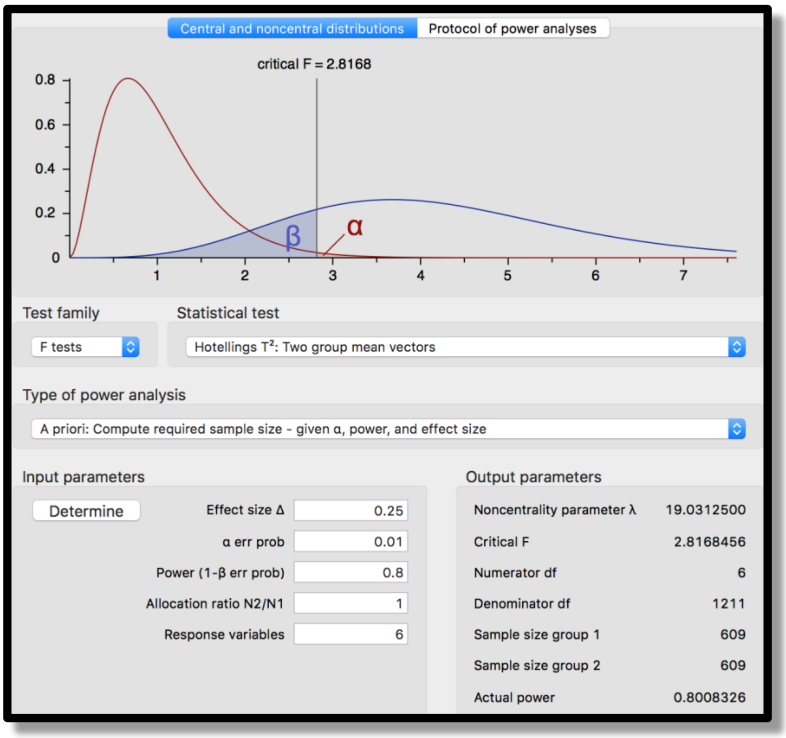

Figure 2.4.d G*Power calculation of required sample size for Hotelling's T^2 test with six dependent variables

Table 2.8 Summary table of sample size requirements

Specific Aim	Statistical Test	Effect Size	Model Variable Assumptions	Total Required
1: Correlates of SDS	Linear regression	$f^2 = 0.02$ (small)	≤ 25 independent variables	1551
2: Correlates of hypnotic use	Logistic regression	OR= 8.08	Normal distribution, r = 0.50	100
			Exponential distribution, r = 0.50	56
			Binomial distribution, r = 0.50	258
			≤ 25 independent variables, r = 0.50, unequal distributions	1250
3: Correlates of SDS change	Linear regression	$f^2 = 0.02$ (small)	≤ 25 independent variables	1551
4: Symptom changes associated with SDS change	Multivariate regression	$f^2 = 0.02$ (small)	≤ 18 dependent variables	1374
4: HRQoL change associated with SDS change	Multivariate regression	$f^2 = 0.02$ (small)	≤ 6 dependent variables	954
4: Symptom change associated with hypnotic use	Hotelling's T^2	$\Delta\bar{\mu}= 0.25$ (small)	≤ 18 dependent variables	1754
4: HRQoL changes associated with hypnotic use	Hotelling's T^2	$\Delta\bar{\mu}= 0.25$ (small)	≤ 6 dependent variables	1218

SDS: sleep disturbance severity; HRQoL: health-related quality of life

2.8 SECTION VIII: STRENGTHS AND LIMITATIONS

2.8.1 Strengths

One of the primary strengths of this study is that it addresses substantial gaps in the literature. Literature on the prevalence and correlates of sleep disturbance in oncology is ample, but difficult to synthesize because of considerable heterogeneity in study populations, methods, covariates, definitions, and measurements. This study allows methodology-consistent comparisons sleep disturbance correlates across cancer types. Furthermore, despite the high prevalence of sleep disturbance in patients with cancer, there is little recent evidence regarding hypnotic use in this population. Patterns of hypnotic use have not been well characterized since the introduction of the current standard-of-care drugs, and there is virtually no evidence regarding their safety and efficacy in persons with cancer. This study provides much needed data that can serve as a point of departure for future research of hypnotics for patients with cancer. Finally, this study adds to the literature on sleep-related symptom clusters by including assessments of symptoms that are less frequently evaluated. Relationships between sleep disturbance and fatigue, pain, and depression are well documented, but there is still much to understand about how other symptoms might relate to sleep. Elucidating these relationships is vital to developing effective and efficient symptom management strategies.

Use of the SOAPP study data provides several advantages, starting with the large and diverse sample size, which will improve the generalizability of findings. At the same time, meaningful comparisons can be made across subpopulations; this has not been possible to date with studies using narrowly defined populations and varied methodologies. The SOAPP data include numerous symptom and health-related quality of life measures that provide for comprehensive and nuanced characterizations of outcomes associated with both sleep disturbance and hypnotic use. A unique feature of the SOAPP study was the inclusion of clinician’s assessments of their patients’ symptoms and quality of life. This information may prove consequential in analyses of hypnotic use patterns. Finally, the two-visit, prospective design of the SOAPP study allows not only for cross-sectional evaluation, but also for assessment of symptom burden changes over a short period of time.

2.8.2 Limitations

Along with the many advantages conferred by the SOAPP study data, there are also some disadvantages. Most notable is the limited detail in characterizing sleep disturbance. The single subjective sleep disturbance measure likely captured a wide variety of sleep disturbances (e.g., restless limbs, apnea, delayed onset, early waking, feeling unrestored), but did not permit distinctions among them. Thus, the outcomes associated with hypnotics can be assessed only in terms of symptom burden and quality of life, rather than sleep-specific parameters.

Detail is also lacking in the documentation of medication use. Among medications commonly used for sleep disturbance, only benzodiazepines and benzodiazepine receptor agonists (BzRAs) are clearly listed. Antidepressants and anticonvulsants are identified as treatments for pain, and the two categories are not broken down into subclasses (e.g., tricyclic antidepressants versus serotonin selective reuptake inhibitors); ramelteon is not listed at all. As a result, only benzodiazepines and BzRAs were included in this study.

Because this is a retrospective, secondary analysis, selection bias cannot be ruled out. Furthermore, although selection of correlates of sleep disturbance was based on a causal model, the cross-sectional design and unknown duration of sleep disturbance (and other variables) prohibit causal inference. Cancer-specific subgroups were not matched in size or demographic characteristics, and important relationships may have gone undetected in the smaller groups due to loss of power. Generalizability of results may be limited to ambulatory patients with solid tumors treated by an Eastern

United States oncology group, and cluster bias could not be controlled for because the data did not identify treatment sites.

The MDASI survey items have been validated in cancer populations, but minimal important differences and severity cut points have not yet been well defined. In addition, the sensitivity of the MDASI survey instrument to assess changes in HRQoL related to sleep has not been evaluated, and surveys are subject to recall bias. Participants were evaluated during the course of treatment, rather than at initiation. This may help to explain the small sizes of change from visit one to visit two as well as the strong bias toward zero in the MDASI response variables.

Finally, it was not possible to determine whether medications prescribed were actually taken, and results may be confounded by undocumented use of other sleep aids, including over-the-counter medications, off-label drugs, and alcohol, or by non-adherence to prescribed hypnotics.

Chapter 3: Manuscripts

This chapter provides three manuscripts that represent the work undertaken for completion of this dissertation project. The three manuscripts report the results from Specific Aims 1, 2, and 4, respectively. Analyses from Specific Aim 3 are not represented, as they yielded no statistically significant model. Only a single level of one variable (primary cancer site: colorectal cancer) correlated significantly with change in sleep disturbance, and it explained only 0.3% of variance. The study may have been underpowered to evaluate the rather small mean change in sleep disturbance (-0.11, on a scale from 0 to 10). This chapter closes with a table of relevant journals to which these manuscripts may be submitted.

3.1 SECTION I: MANUSCRIPT 1

Sleep Disturbance Prevalence and Correlates in Solid Tumor Cancers

Introduction

Disturbed sleep is among the commonest and most severe symptoms reported by patients with cancer.[82,90,110] In addition to reducing health-related quality of life,[87,91,111] disturbed sleep can exacerbate other cancer symptoms[81,137] and may worsen prognoses.[88,89] For well over a decade, oncology clinicians and researchers have recognized sleep disturbance to be widespread and impactful for their patients,[218,219] yet to date, evidence to guide treatment is scant.[156,164]

Many risk factors for sleep disturbance in the oncology setting have been identified,[166] but the relative importance of these factors is not well characterized and the pathophysiology remains undetermined.[219] Literature on the prevalence and correlates of sleep disturbance in oncology is ample, but difficult to synthesize because of considerable heterogeneity in study populations, methods, covariates, definitions, and measurements. Recent study samples, for example, include twenty-nine newly diagnosed breast cancer patients,[220] fifty patients with lung cancer,[221] 440 patients receiving palliative care for advanced cancer,[222] and 105 patients scheduled to receive radiotherapy.[223] No two studies used the same sleep disturbance measures, nor were covariate selection and measurement consistent. Findings from these studies further exemplify interpretive challenges: Nishiura et. al. found sleep disturbance associated with chemotherapy in patients with lung cancer,[221] while Yennurajalingam et. al. found no such association in patients with advanced cancer.[222] Because neither analysis controlled for covariates, it is difficult to evaluate whether other characteristics in these disparate samples might explain the contradiction.

Many disease and treatment characteristics (e.g., pain, fatigue, chemotherapy) are fairly ubiquitous among solid tumor cancers, but some are specific to certain cancer types (e.g., hormone therapy for breast or prostate cancer). Accordingly, one can expect sleep disturbance correlates to be similarly distributed in the oncology setting. Distinguishing cancer type-specific sleep disturbance factors from those that are universal may shed light on underlying mechanisms and inform both general guidelines and patient-specific interventions. Data and analyses that are comparable across cancer subtypes are integral to building such understanding.

This study aims to identify – from a large number of demographic, clinical, treatment, and symptom variables – the most significant correlates of sleep disturbance in a large diverse sample of persons with cancer, and to replicate the analyses in cancer-specific subgroups.

Methods

This was a secondary analysis of the Symptom Outcomes and Practice Patterns (SOAPP) study conducted from March 3, 2006 to May 19, 2008 in about 40 clinics located primarily in the Eastern United States. Outpatients at least 18 years of age at any stage of care for invasive breast, lung, prostate, or colorectal cancer were eligible to participate; respondents with inadequate cognitive function (assessed by a study screener) were excluded.[171] At the first visit, clinicians and patients provided, respectively, clinical and demographic data. Additionally, patients scored their baseline symptom severity for nineteen cancer symptoms. For the present analysis, cases missing a severity score for sleep disturbance were excluded.

Study variables

Sleep disturbance. The SOAPP study used an expanded (19-item, see **Table 3.1**) version of the 13-item MD Anderson Symptom Inventory (MDASI), which asks patients to rate symptoms (including 'disturbed sleep') at their worst in the last 24 hours.[224] Symptom severity is scaled from 0='Not present' to 10='As bad as you can imagine,' and standard deviations ranged from 1.95 to 2.31 in validation studies, and the MDASI developers suggest a 1-point change may be minimally important (i.e., clinically significant).[175] In a systematic review of health-related quality of life studies, the detection threshold for meaningful change was, in many cases, one-half standard deviation.[176] There is no consensus yet, however, on an ideal method for determining clinical significance, and even a consistent method may yield different results across subpopulations.[177,225] Nevertheless, the present study assumes a 1-point difference in symptom severity to be clinically meaningful.

Correlates of sleep disturbance. Selection of correlates was based on the '3P' model of insomnia, which characterizes risk factors as predisposing, precipitating, and/or perpetuating.[†] Predisposing factors for insomnia include physiological, psychological, or social circumstances that increase one's vulnerability to sleep disruption; precipitating factors are life events that trigger acute insomnia; and perpetuating factors inhibit one's ability to adapt and resume normal sleeping patterns.[183] The SOAPP study measured numerous variables, allowing for broad exploration of potential sleep disturbance correlates. Interpretation is limited, however, by lack of information pertaining to timing. For example, initiation of treatment (e.g., chemotherapy, corticosteroids) may precipitate sleep disturbance, while continued treatment may perpetuate sleep disturbance. Because timing data (initiation and duration) are mostly unavailable in this study, distinctions between precipitation and perpetuation cannot be made, nor can causality be inferred. Therefore, factors will be treated as correlates only. **Table 3.1** lists study variables included in saturated models.

[†] The terms *sleep disturbance* and *insomnia* are often used interchangeably to describe difficulty falling asleep, staying asleep, and/or dissatisfaction with one's sleep quality. It should be noted, however, that diagnostic criteria for insomnia are more specific, and include daytime sequelae, while the term *sleep disturbance* may encompass a wider range of complaints (e.g., restless leg syndrome, obstructive sleep apnea).

Statistical methods

Software. Statistical analyses were conducted using the following software: Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.), SAS (SAS Institute. 2015. The SAS system for Windows. Release 9.4. SAS Institute, Cary, NC.), Excel (Microsoft®. 2015. Excel for Mac. Version 15) and IVEware (University of Michigan. 2002. IVEware: Imputation and Variance Estimation Software).

Data reduction. For visualization and bivariate analysis, but not regression modeling, participants were grouped by reported sleep disturbance severity: None (0), Mild (1-4), Moderate (5-6), and Severe (7-10). Although prior findings are not conclusive, cut-points of 5 and 7 are often identified as clinically meaningful thresholds for cancer symptom assessments using 0 to 10 scales (e.g., Edmonton Symptom Assessment Scale, Brief Fatigue Inventory, Brief Pain Inventory).[179,180,182]

Missing data analysis. The percentage of missing values was low (<4%) for most independent variables, except ethnicity (7.18%), current hormone therapy (16.25%), and current immunotherapy (18.35%). With a large number of variables, however, list-wise deletion would reduce the sample by about 25%. Using SAS software and a callable routine built with IVEWare, values were multiply-imputed ($m=5$) through sequential multiple regression by chained equations to accommodate heterogeneity of variable type and distribution.[201-203] Results of statistical tests were pooled using Excel spreadsheets for ANOVA,[226] and the *mi estimate* command in Stata for regression analysis. Comparison of imputed datasets by analysis of variance (ANOVA) revealed no differences for any variables, except current hormone therapy ($F=5.54$ [1,13903], $p = 0.0186$). Final regression analyses were, therefore, performed on a singly-imputed dataset, to permit use of additional analytic procedures, including regression diagnostics.

Table 3.1 Correlates included in saturated regression models

Demographic variables	**Clinical variables**	**Treatment variables**	**Symptom care medications**
Age	Primary site	Clinician	Long- & mid- acting benzodiazepines
Sex	*Breast*	*Attending Physician*	Short-acting benzodiazepines
Male	*Colorectal*	*Resident or fellow*	Benzodiazepines receptor agonists
Female	*Prostate*	*Advanced practice nurse / nurse practitioner*	Steroids
Race	*Lung*	*Physician assistant*	Tricyclic antidepressants
White	Months since diagnosis	*Other*	Anticonvulsants for pain
Black	Cancer stage	Prior radiotherapy	Antidepressants for pain
*Other**	*No evidence of disease*	Current radiotherapy	Promethazine
Ethnicity	*Local/regional*	Prior number of regimens	Neurokinin-1 inhibitors
Hispanic	*Metastatic*	*None*	Metoclopramide
Non-Hispanic	*Local/regional/metastatic*	*1*	5-HT3 antagonists
Employment status	Cancer status	*2*	Allergy medications
Part-time	*Disappearance*	*3 or more*	Misc anxiolytics / antidepressants
Full-time	*Partial response*	Current chemotherapy	
Not employed	*Stable*	*None*	**Symptom severity scores**
Employment change in last 4 weeks	*Progression*	*Systemic single*	Alopecia (hair loss)
	ECOG performance status	*Systemic multi*	Anorexia (lack of appetite)
Driving in last 4 weeks	*0*	*Nonsystemic / Noncytotoxic*	Cognitive difficulty (remembering)
History of depression	*1*	Current immunotherapy	Constipation
Family history of depression	*2*	Current hormone therapy	Cough
	3 & 4	Current treatment stage	Depressed (feeling sad)
	Cognitive function	*None*	Diarrhea (loose stools)
	No impairment	*Adjuvant*	Distressed (upset)
	Partial impairment	*Non-metastatic*	Drowsy (sleepy)
	Pain mechanism	*Metastatic*	Dyspnea (shortness of breath)
	None	Attending support group	Fatigue (tiredness)
	Nociceptive	Attending counseling	Nausea
	Neuropathic	Pain treatment	Neuropathy (numbness & tingling)
	Psychological distress	*None*	Pain
		Opioids	Stomatitis (mouth sores)
		Non-opioids	Urticaria (skin rash)
		Combination	Vomiting
			Xerostomia (dry mouth)

Statistical analyses. Summary statistics are reported for the overall sample and for each sleep disturbance severity (SDS) group. The sample was then subdivided by cancer type and subsample characteristics were evaluated using ANOVA and chi-squared tests. Because SDS scores are discrete and strongly skewed toward zero, non-parametric models (including Poisson, zero-inflated Poisson, ordinal logistic, and zero-inflated beta) were initially evaluated, but linear regression analysis produced the best-fitting models. The final linear regression model was subjected to diagnostic tests for multicollinearity (variance inflation factors < 3.0 for all variables), outliers and highly influential observations (largest Cook's distance = 0.018), normality of residuals (kernel density plot, Appendix A and homoscedasticity (Breusch-Pagan test, $p<0.001$). The test for homoscedasticity failed; therefore, robust standard errors were computed for improved validity.[206] Saturated models were reduced based on significance level for each correlation coefficient and model fit was evaluated with Bayesian Information Criterion values. After modeling the total sample, cancer site-specific models were evaluated using the same methods. To mitigate Type I error risk from multiple analyses, we used a significance cutoff of $p<0.01$.

Results

Sample characteristics

Overall sample. Of 3,106 participants in the SOAPP study, 2,382 had sleep disturbance severity (SDS) scores. The sample was 71% female, 86% white, and mean age was 61 years (range, 23 to 93 years). The majority (62.8%) reported some degree of disturbed sleep **[Figure 3.2],** with about one quarter (26.2%) scoring the severity as moderate to severe (SDS≥5). **Table 3.2** shows sample characteristics overall and by sleep disturbance severity group.

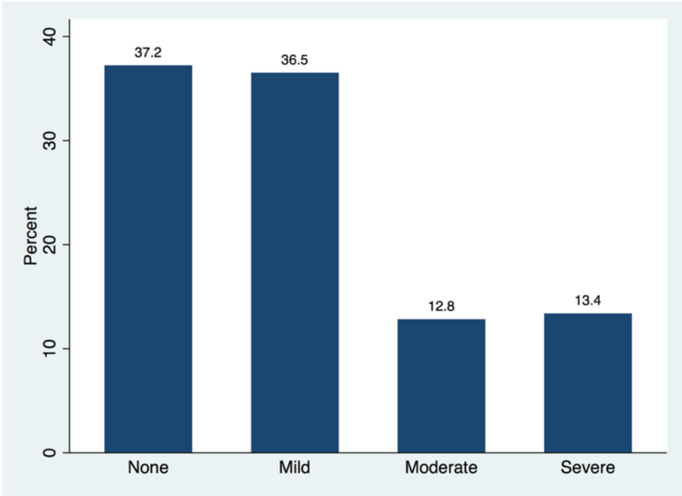

Figure 3.1 Distribution of subjective scores for severity of disturbed sleep at its worst in the last 24 hours: None (rating=0), Mild (rating=1-4), Moderate (rating=5-6), and Severe (rating=7-10)

Cancer site-specific groups. Primary cancer sites were: breast (51%), colorectal (24%), lung (15%), and prostate (10%). **Table 3.3** shows subsample characteristics for each cancer site. On average, breast cancer patients were youngest (57.6 ± 11.4 years), and prostate cancer patients were oldest (71.0 ± 9.5 years; $F[3,2378]=109.47$; $p<0.001$). No gender difference was detected between lung and colorectal cancer (evaluated separately from breast and prostate cancer). Groups differed by Hispanic/non-Hispanic ethnicity ($X^2[3]=23.96;p<0.001$), but not race. Cancer disappearance was most common for breast cancer, while lung and prostate cancer had higher frequencies of partial response, progression, and stable disease ($X^2[9]=308.43;p<0.001$).

Time since diagnosis was different across all groups ($F[3,2378]=56.31$; $p<0.001$), except between lung and prostate cancer. Benzodiazepine receptor agonist use was lowest in prostate (3.8%) and colorectal (4.6%) cancer, and highest in lung cancer (9.4%; $X^2[3]=542.39;p=0.007$). Comparing only breast and prostate cancer, hormone therapy was significantly higher for prostate cancer (59.9% versus 37.5%); $X^2[1]=41.29;p<0.001$). Finally, cancer-specific differences were seen among all symptoms that appeared in models (see **Table 3.3** for pairwise relationships). Groups sizes were uneven, and fewer significant correlates were identified in smaller groups.

Table 3.2 Sample characteristics overall and stratified by severity of disturbed sleep

	TOTAL SAMPLE	Sleep not Disturbed	Sleep Mildly Disturbed	Sleep Moderately Disturbed	Sleep Severely Disturbed		
TOTAL SAMPLE	**N (%)** **2382 (100.0)**	**N (%)** **887 (37.2)**	**N %)** **807 (36.5)**	**N %)** **306 (12.6)**	**N (%)** **319 (13.4)**	***F***	***p***
AGE, YEARS							
Mean	**60.9**	62.8	60.7	60.2	57.0		
Std. Deviation	**(12.2)**	(12.3)	(11.8)	(12.0)	(12.4)	18.55	<0.001*
SEX						***X^2***	***p***
Male	**693 (29.1)**	271 (30.6)	251 (28.9)	92 (30.1)	79 (24.8)		
Female	**1689 (70.9)**	616 (69.4)	619 (71.2)	214 (69.9)	240 (75.2)	3.98	0.264
RACE							
White	**2052 (86.1)**	750 (84.6)	789 (90.7)	264 (86.3)	247 (77.4)		
Black	**283 (11.9)**	118 (13.3)	71 (8.2)	33 (10.8)	62 (19.4)		
Other	**47 (2.0)**	19 (2.1)	10 (1.2)	9 (2.9)	10 (3.1)	39.47	<0.001*
ETHNICITY							
Hispanic	**187 (8.1)**	89 (10.0)	50 (5.8)	17 (5.6)	37 (11.6)		
Non-Hispanic	**2195 (91.9)**	798 (90.0)	820 (94.3)	289 (94.4)	282 (88.4)	16.45	0.001*
PRIMARY SITE							
Breast	**1212 (50.9)**	429 (48.4)	450 (51.7)	155 (50.7)	178 (55.8)		
Colorectal	**570 (23.9)**	237 (26.7)	204 (23.5)	71 (23.2)	58 (18.2)		
Prostate	**237 (10.0)**	97 (10.9)	83 (9.5)	31 (10.1)	26 (8.2)		
Lung	**363 (15.2)**	124 (14.0)	133 (15.3)	49 (16.0)	57 (17.9)	14.74	0.098
CANCER STATUS							
Disappearance	**908 (38.1)**	375 (42.3)	327 (37.6)	96 (31.4)	110 (34.5)		
Partial response	**122 (5.1)**	38 (4.3)	46 (5.3)	18 (5.9)	20 (6.3)		
Stable	**1029 (43.2)**	371 (41.8)	372 (42.8)	141 (46.1)	145 (45.5)		
Progression	**323 (13.6)**	103 (11.6)	125 (14.4)	51 (16.7)	44 (13.8)	16.89	0.050
HYPNOTIC USE							
None	**1822 (76.5)**	757 (85.3)	660 (75.9)	203 (66.3)	202 (63.3)	95.37	<0.001*
BzRA	**156 (6.6)**	27 (3.0)	57 (6.6)	35 (11.4)	37 (11.6)	7.80	0.253†
Short-acting BZD	**229 (9.6)**	62 (7.0)	89 (10.2)	37 (12.1)	41 (12.9)		
Long-/Intermediate- acting BZD	**175 (7.4)**	41 (4.6)	64 (7.4)	31 (10.1)	39 (12.2)		

† A secondary analysis of hypnotic use only revealed no difference in hypnotic use by class.

Table 3.3 Sample characteristics overall and for cancer-specific subgroups, including all significant correlates

		Total Sample N	(%)	Breast Cancer N	(%)	Colorectal Cancer N	(%)	Lung Cancer N	(%)	Prostate Cancer N	(%)	X^2 Test	*p*-value
		2382	**(100.0)**	**1212**	**(50.9)**	**570**	**(24.0)**	**363**	**(15.2)**	**237**	**(10.0)**		
Sex	*Male*	**693**	**(29.1)**	3	(0.2)	293	(51.4)	160	(44.1)	237	(100.0)	1200	<0.001
	Female	**1689**	**(70.9)**	1209	(99.8)	277	(48.6)	203	(55.9)	0	(0.0)	4.77*	0.029*
Race	*White*	**2052**	**(86.2)**	1064	(87.8)	473	(83.0)	316	(87.1)	199	(84.0)	12.33	0.055
	Black	**283**	**(11.9)**	126	(10.4)	85	(14.9)	37	(10.2)	35	(14.8)		
	Other	**47**	**(2.0)**	22	(1.8)	12	(2.1)	10	(2.8)	3	(1.3)		
Ethnicity	*Hispanic*	**187**	**(7.9)**	83	(6.9)	65	(11.4)	13	(3.6)	26	(11.0)	23.96	<0.001
	Non-Hispanic	**2195**	**(92.2)**	1129	(93.2)	505	(88.6)	350	(96.4)	211	(89.0)		
Cancer status	*Disappearance*	**909**	**(38.2)**	642	(53.0)	194	(34.0)	42	(11.6)	31	(13.1)	308.43	<0.001
	Partial response	**120**	**(5.0)**	35	(2.9)	25	(4.4)	37	(10.2)	23	(9.7)		
	Stable	**1030**	**(43.2)**	420	(34.7)	256	(44.9)	221	(60.9)	133	(56.1)		
	Progression	**323**	**(13.6)**	115	(9.5)	95	(16.7)	63	(17.4)	50	(21.1)		
BzRA use	*No*	**2226**	**(92.8)**	1125	(92.8)	544	(95.4)	329	(90.6)	228	(96.2)	12.10	0.007
	Yes	**156**	**(7.2)**	87	(7.2)	26	(4.6)	34	(9.4)	9	(3.8)		
Hormone therapy	*No*	**1779**	**(74.7)**	758	(62.5)	566	(99.3)	360	(99.2)	95	(40.1)	542.39	<0.001
	Yes	**603**	**(25.3)**	454	(37.5)	4	(0.7)	3	(0.8)	142	(59.9)	41.29	<0.001**
Anticonvulsants	*No*	**2237**	**(93.9)**	1142	(94.2)	540	(94.7)	331	(94.5)	224	(91.2)	5.76	0.124
	Yes	**145**	**(6.1)**	70	(5.8)	30	(5.3)	13	(5.5)	32	(8.8)		

* A secondary evaluation of sex and cancer site was performed for the colorectal and lung cancer groups only.
** A secondary evaluation of hormone therapy and cancer site was performed for the breast and prostate cancer groups only.

Table 3.3 (continued) Sample characteristics overall and for cancer-specific subgroups, including all significant correlates

		Total Sample		**Breast Cancer**		**Colorectal Cancer**		**Lung Cancer**		**Prostate Cancer**		***F*-test**	***p*-value**
		Mean	**(SE)**	**Mean**	**(SE)**	**Mean**	**(SE)**	**Mean**	**(SE)**	**Mean**	**(SE)**		
Age (years)[a]		**60.91**	**(0.25)**	57.57	(0.33)	61.37	(0.53)	64.74	(0.56)	70.99	(0.62)	109.47	<0.001
Years since diagnosis		**2.88**	**(0.09)**	3.49	(0.14)	1.83	(0.09)	1.30	(0.09)	4.67	(0.30)	56.31	<0.001
Symptom severity	*Disturbed sleep*	**2.58**	**(0.06)**	2.69 [c]	(0.09)	2.26 [b,l]	(0.12)	2.86 [c]	(0.16)	2.38	(0.18)	4.43	0.004†
	Cognitive difficulty	**1.95**	**(0.05)**	2.03	(0.07)	1.71 [l]	(0.10)	2.25 [c]	(0.13)	1.66	(0.14)	5.40	0.001
	Constipation	**1.42**	**(0.05)**	1.33	(0.07)	1.30	(0.10)	2.03 [a]	(0.15)	1.18	(0.14)	9.06	<0.001
	Cough	**1.18**	**(0.04)**	0.98	(0.05)	0.91	(0.08)	2.43 [a]	(0.14)	0.95	(0.14)	51.84	<0.001
	Distress	**1.96**	**(0.05)**	2.02 [l]	(0.08)	1.79	(0.11)	2.37 [b,l]	(0.14)	1.40 [l]	(0.15)	7.75	<0.001
	Drowsiness	**2.42**	**(0.05)**	2.35	(0.08)	2.34	(0.11)	2.96 [a]	(0.14)	2.19	(0.15)	6.14	0.004
	Fatigue	**3.29**	**(0.06)**	3.16	(0.08)	3.17	(0.12)	4.07 [a]	(0.15)	3.02	(0.19)	10.72	<0.001
	Nausea	**0.93**	**(0.04)**	0.83	(0.06)	1.17 [p]	(0.09)	1.20 [p]	(0.11)	0.47 [c,l]	(0.08)	9.98	<0.001
	Pain	**1.89**	**(0.06)**	1.87	(0.08)	1.74	(0.11)	2.31	(0.15)	1.66	(0.17)	4.10	0.007†
	Anorexia	**1.46**	**(0.05)**	1.19 [c,l]	(0.07)	1.68 [b]	(0.11)	2.20 [b,l]	(0.15)	1.12 [l]	(0.15)	18.29	<0.001
	Neuropathy	**2.05**	**(0.06)**	1.79 [c]	(0.08)	2.72 [b,p]	(0.13)	2.10	(0.14)	1.68 [c]	(0.16)	15.88	<0.001

† Pairwise comparisons did not meet p < 0.01 level of significance.
a-p Significantly different (p<0.001) in post-hoc Scheffe pairwise contrasts (comparison to a: all; b: breast: c: colorectal; l: lung; p: prostate).
BzRA: benzodiazepine receptor agonist

Models for sleep disturbance

Overall sample (N=2,382). The best-fitting model [**Table 3.4]** accounted for 43.4% of variance in SD severity scores (F(10,2371)=180.34; $p<0.001$; adj $R^2=0.434$; BIC'=-1288.363). Significant correlates were: age, benzodiazepine receptor agonist (BzRA) use, and eight cancer symptoms (cognitive difficulty, constipation, cough, distress, drowsiness, fatigue, nausea, pain).

Breast cancer (N=1,212). The best-fitting model [**Table 3.4a**] accounted for 46.1% of variance (F(8,1203)=152.57; $p<0.001$; adj $R^2=0.461$; BIC'=-700.014). Significant correlates were: age, hormone therapy, and six cancer symptoms (cognitive difficulty, cough, distress, drowsiness, fatigue, nausea)

Colorectal cancer (N=570). The best-fitting model [**Table 3.4b**] accounted for 48.2% of variance (F(7,562)=67.09; $p<0.001$; adj R2=0.482; BIC'=-337.644). Significant correlates were: stable disease status and four symptoms (anorexia, distress, fatigue, pain).

Lung cancer (N=363). The best-fitting model [**Table 3.4c**] accounted for 37.1% of variance (F(4,358)=54.78; $p<0.001$; adj R2=0.371; BIC'=-148.805). Only four symptoms were significant correlates (cognitive difficulty, constipation, distress, neuropathy).

Prostate cancer (N=237). The best-fitting model [**Table 3.4d**] accounted for 27.2% of variance (F(3,233)=30.03; $p<0.001$; adj R2=0.272; BIC'=-61.981). Significant correlates were: anticonvulsant use for pain, and two symptoms (distress, drowsiness).

Table 3.4 Model for correlates of sleep disturbance in a large sample of persons with breast, lung, colorectal, and prostate cancer

Total sample (n=2382)	**N**	**(%)**	**Regression Coefficient**	**Robust Std. Error**	**Standardized Regr. Coeff.**	***p*-value**
Benzodiazepine receptor agonist use						
No	2226	(93.6)				
Yes	156	(6.6)	0.714	(0.195)	*0.061*	<0.001
	Mean	**(SD)**				
Age	60.91	(0.25)	-0.015[a]	(0.004)	*-0.061[a]*	<0.001
Symptom severity scores						
Cognitive difficulty	1.95	(0.05)	0.108	(0.028)	*0.089*	<0.001
Constipation	1.41	(0.05)	0.073	(0.027)	*0.063*	0.006
Cough	1.18	(0.04)	0.100	(0.029)	*0.074*	0.001
Distress	1.96	(0.05)	0.302	(0.030)	*0.270*	<0.001
Drowsiness	2.42	(0.05)	0.091	(0.033)	*0.083*	0.006
Fatigue	3.29	(0.06)	0.150	(0.030)	*0.149*	<0.001
Nausea	0.93	(0.04)	0.087	(0.032)	*0.060*	0.007
Pain	1.89	(0.06)	0.095	(0.028)	*0.088*	0.001

$F(10,2371)=180.34$; $p<0.001$; adj $R^2=0.434$; BIC'=-1288.363

a. Coefficients for age are shown for one-year units. For a 10-year increase in age, the regression coefficient (*b)* goes to -0.15 and the standardized regression coefficient (β) goes to -0.61.

Table 3.4a Model for correlates of sleep disturbance for participants with breast cancer

4a. Breast cancer (n=1212)	**N**	**(%)**	**Regression Coefficient**	**Robust Std. Error**	**Standardized Regr. Coeff.**	***p*-value**
Hormone therapy						
No	758	(62.5)				
Yes	454	(37.5)	0.386	(0.131)	*0.063*	0.003
	Mean	**(SD)**				
Age	57.57	(0.39)[b]	-0.023	(0.006)	*-0.089*[b]	<0.001
Symptom severity scores						
Cognitive difficulty	2.03	(0.07)	0.119	(0.038)	*0.097*	0.002
Cough	0.98	(0.06)	0.114	(0.043)	*0.076*	0.009
Distress	2.02	(0.08)	0.333	(0.041)	*0.300*	<0.001
Drowsiness	2.35	(0.08)	0.118	(0.045)	*0.107*	0.010
Fatigue	3.16	(0.08)	0.211	(0.043)	*0.203*	<0.001
Nausea	0.83	(0.06)	0.136	(0.044)	*0.089*	0.002

$F(8,1203)=152.57$; $p<0.001$; adj $R^2=0.461$; BIC'=-700.014

b. Coefficients for age are shown for one-year units. For a 10-year increase in age, the regression coefficient (*b*) goes to -0.23 and the standardized regression coefficient (β) goes to -0.89.

Table 3.4b Model for correlates of sleep disturbance for participants with colorectal cancer

4b. Colorectal Cancer (N=570)	**N**	**(%)**	**Regression Coefficient**	**Robust Std. Error**	**Standardized Regr. Coeff.**	***p*-value**
Clinical status						
Disappearance	194	(34.04)				
Partial response	25	(4.39)	-0.690	(0.498)	*-0.052*	0.166
Stable	256	(44.91)	-0.532	(0.186)	*-0.096*	0.004
Progression	95	(16.67)	-0.220	(0.240)	*-0.030*	0.360
	Mean	**(SD)**				
Symptom severity scores						
Anorexia	1.68	(0.11)	0.216	(0.050)	*0.210*	<0.001
Distress	1.79	(0.11)	0.286	(0.052)	*0.265*	<0.001
Fatigue	3.17	(0.12)	0.183	(0.048)	*0.192*	<0.001
Pain	1.74	(0.11)	0.251	(0.054)	*0.247*	<0.001

$F(7,562)=67.09$; $p<0.001$; adj $R^2=0.482$; BIC'=-337.644

Table 3.4c Model for correlates of sleep disturbance for participants with lung cancer

4c. Lung Cancer (N=363)	**Mean**	**(SD)**	**Regression Coefficient**	**Robust Std. Error**	**Standardized Regr. Coeff.**	***p*-value**
Symptom severity scores						
Cognitive difficulty	2.26	(0.13)	0.204	(0.071)	*0.174*	0.004
Constipation	2.03	(0.15)	0.178	(0.052)	*0.175*	0.001
Distress	2.37	(0.14)	0.389	(0.069)	*0.347*	<0.001
Neuropathy	2.10	(0.15)	0.196	(0.059)	*0.182*	0.001

$F(4,358)=54.78$; $p<0.001$; adj $R^2=0.371$; BIC'=-148.805

Table 3.4d Model for correlates of sleep disturbance for participants with prostate cancer

4d. Prostate Cancer (N=237)	**N**	**(%)**	**Regression Coefficient**	**Robust Std. Error**	**Standardized Regr. Coeff.**	***p*-value**
Anticonvulsant for pain						
No	224	(94.51)				
Yes	13	(5.49)	-1.329	-0.394	*-0.107*	0.001
	Mean	**(SD)**				
Symptom severity scores						
Distress	1.40	(0.15)	0.475	-0.078	*0.377*	<0.001
Drowsiness	2.19	(0.15)	0.301	-0.085	*0.250*	<0.001

$F(3,233)=30.03$; $p<0.001$; adj $R^2=0.272$; BIC'=-61.981

Correlates of sleep disturbance

Table 3.5 provides an overview of sleep disturbance severity (SDS) correlates in each model, along with corresponding regression coefficients and standardized coefficients. Consistency in measurement methods permits comparison of relative importance for each correlate across models.

Demographic characteristics

In addition to age, sex, race, and ethnicity, we evaluated driving status, employment status, recent employment change, and personal and family history of depression. We found no associations with any demographic variable except age.

In bivariate analyses, Black and Hispanic participants were more likely to report either no sleep disturbance or severe sleep disturbance than their white and non-Hispanic counterparts [Table 3.2], but these findings did not persist in regression models and may reflect response bias, rather than actual differences. Studies have shown that Hispanics and blacks in the United States have a higher tendency to respond at the extreme ends of Likert-type response scales than non-Hispanics and whites.[227-230]

Age. In the overall sample, older age correlated with decreased SDS scores (b=-0.015; β=-0.061; p<0.001). In sub-analysis by cancer site, however, age correlated with SDS for breast cancer only (b=-0.023; β=-0.089; p=0.003). The overall finding likely reflects the breast cancer cohort, which comprised 50.9% of the total sample; without this group, age no longer correlated with SDS overall. The breast cancer group is distinct for being 99.8% female. Sex did not correlate with SDS in any model in this study, but females have greater risk of insomnia in general.[31]

Clinical characteristics

Site of primary cancer did not correlate with SDS, nor did cancer stage or ECOG performance status.* Also evaluated were: pain duration, pain mechanism, psychological distress (evaluated by clinician), cognitive function, and disease status. No clinical characteristic correlated with SDS overall; for participants with colorectal cancer, stable disease status (versus disappearance) correlated with decreased SDS (b=-0.532; β=-0.096; p=0.041).

Treatment characteristics

No associations were found with clinician type, support group, counseling, and pain treatment. Among cancer-specific therapies (chemotherapy and radiotherapy [current and prior], immunotherapy, hormone therapy, treatment stage, and prior number of regimens), only hormone therapy correlated with SDS, and only for breast cancer (b=0.386; β=0.063; p=0.003). (NB: frequency of hormone therapy was negligible (<1%) for colorectal and lung cancers.)

Supportive medications

Among many medications prescribed for symptom management, our analysis included only those with documented effects on sleep [Table1]. Of special interest are the sedative-hypnotic benzodiazepines [BZDs] (e.g., temazepam, clonazepam) and benzodiazepine receptor agonists [BzRAs] (e.g., zolpidem, zaleplon), classically used to treat sleep disturbances. In the overall sample, BzRA use correlated with increased SDS (b=0.714; β=0.061; p<0001), but no other associations (positive or negative) were found for sedative-hypnotics.

A noteworthy finding was substantially decreased SDS (b=-1.329; β=-0.107; p=0.001) among participants with prostate cancer using anticonvulsants for pain (e.g., gabapentin, pregabalin, which have known hypnotic effects); among all models, this was the largest regression coefficient.

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* Eastern Cooperative Oncology Group (ECOG) Performance Status grading system[231] starts at 0 for 'fully active without restriction'. Increasing scores represent worsening functional status (up to 5 = death). Because of small sample size, grades 3 and 4 were evaluated together.

Table 3.5 Comparison of regression coefficients (b) and standardized regression coefficients (β) for models of sleep disturbance, overall and by cancer type

		All Cancer Sites N = 2,382		***Breast Cancer*** N = 1,212		***Colorectal Cancer*** N = 570		***Lung Cancer*** N = 363		***Prostate Cancer*** N = 237	
		b	***β***	***b***	***β***	***b***	***β***	***b***	***β***	***b***	***β***
Symptom severity	*Distress*	0.302	*0.270*	0.333	*0.300*	0.286	*0.265*	0.389	*0.347*	0.469	*0.373*
	Fatigue	0.150	*0.149*	0.211	*0.203*	0.183	*0.192*				
	Cognitive problems	0.108	*0.089*	0.119	*0.097*			0.204	*0.174*		
	Pain	0.092	*0.088*			0.251	*0.247*				
	Drowsiness	0.091	*0.083*	0.118	*0.107*					0.319	*0.265*
	Cough	0.100	*0.074*	0.114	*0.076*						
	Constipation	0.073	*0.063*					0.178	*0.175*		
	Nausea	0.087	*0.060*	0.136	*0.089*						
	Anorexia					0.216	*0.210*				
	Neuropathy							0.196	*0.182*		
Age		-0.015[a]	*-0.061*[b]	-0.023[a]	*-0.089*[b]						
BzRA use		0.714	*0.061*								
Hormone therapy				0.386	*0.063*						
Clinical status	*Stable*					-0.532	*-0.096*				
Anticonvulsants for pain										-1.329	*-0.107*

b: Regression coefficient.

β: Standardized regression coefficient.

a. Coefficients for age are shown for one-year units. For a 10-year increase in age, the regression coefficient (*b)* goes to -0.15 and the standardized regression coefficient (β) goes to -0.61.

b. Coefficients for age are shown for one-year units. For a 10-year increase in age, the regression coefficient (b) goes to -0.23 and the standardized regression coefficient (β) goes to -0.89.

Cancer symptoms

In addition to disturbed sleep, eighteen other symptoms [**Table 3.1**] were evaluated. Among cancer types, symptom severity scores were often highest in the lung cancer group and lowest in the prostate cancer group [**Table 3.3**]. *Distress* was the only symptom that correlated with SDS in all models; it also had the largest standardized regression coefficient in each model (overall: b=0.302; β=0.270;p<0.001).

- *Fatigue* was scored most severe (on average) in all groups, and correlated with SDS overall and for breast and colorectal cancer (overall: b=0.150; β=0.149; p<0.001).
- *Pain* correlated with SDS overall and in colorectal cancer (overall: b=0.095; β=0.88; p=0.001).
- *Drowsiness* correlated with SDS overall and in breast and prostate cancer (overall: b=0.091; β=0.083; p=0.006).
- *Nausea* correlated with SDS overall and in breast cancer (overall: b=0.087; β=0.060; p=0.007).
- *Cough* correlated with SDS overall and in breast cancer (overall: b=0.100; β=0.074; p=0.001).
- *Anorexia* correlated with SDS for colon cancer only (b=0.216; β=0.210; p<0.001).
- *Neuropathy* correlated with SDS for lung cancer only (b=0.196; β=0.182; p=0.001).

Discussion

We aimed to identify significant correlates of sleep disturbance among a broad array of variables and in a clinically and demographically diverse sample of persons with cancer. Most previous studies have focused on narrower patient populations (e.g., women with breast cancer, patients undergoing chemotherapy, patients with advanced disease) and/or have evaluated a more limited set of covariates. In addition, variability in methods and measures across studies complicates interpretation of the aggregate literature. In the present study, we evaluated a large sample in its entirety, as well as in cancer-specific partitions. Consistent measurement across these analyses permits more meaningful comparisons of the relative importance of each correlate.

Prevalence of sleep disturbance

In our large sample (N=2,382) of patients with breast, colorectal, lung, or prostate cancer, 62.8% reported some degree of disturbed sleep, and 26.2% scored their sleep disturbance as moderate to severe (≥5 on a scale of 0='not present' to 10='as bad as you can imagine'). Previous studies of large mixed cancer samples report similar results. Stepanski et. al. found 55% of participants (N=11,445) had trouble sleeping, and 26% classified their sleep troubles as moderate to severe;[81] 80% of chemotherapy (N=823) recipients evaluated by Palesh et. al. reported disturbed sleep and 43% met the diagnostic criteria for insomnia;[80] and Romito et. al. classified 66% of chemotherapy recipients (N=403) as bad sleepers.[93]

Cancer symptoms and sleep disturbance

In modeling correlates of sleep disturbance, our most prominent finding was the overwhelming relationship between cancer symptoms and disturbed sleep. Initial regression models were saturated with numerous factors, including cancer symptoms, demographic and clinical characteristics, cancer treatment variables, and medication use. Final regression models, however, consisted primarily of cancer symptoms, and only five non-symptom factors correlated with SDS. In separate analyses [Appendix B], models tested without symptom variables accounted for only 10% to 19% of SDS variance (and no model resolved for prostate cancer); with symptoms included, models accounted for between 27% and 48% of SDS variance. Although symptoms figure substantially in each model, the mixture of symptoms is inconsistent across cancer types, and some associations were unexpected. Cough correlated with SDS in breast cancer, but not lung cancer (despite significantly higher cough severity scores in the lung cancer group). Constipation correlated with SDS in lung cancer, but no gastrointestinal symptoms correlated with SDS in colorectal cancer (despite significantly higher diarrhea severity scores).

It is noteworthy that severity of symptoms did not dictate models. For example, in the lung cancer group, average pain severity was higher than in any other group, and the most severe-rated symptom was fatigue; yet neither fatigue nor pain correlated with SDS in participants with lung cancer. Similarly, despite the prominence of cancer symptoms in models, the magnitude of association (indicated by regression coefficients) is modest for individual symptoms. Conceivably, generally low severity scores across symptoms may have restricted the effect size range of our models. Nonetheless, our findings suggest that, even when symptoms are fairly well-controlled, clinically important relationships between sleep and other symptoms may be present. Furthermore, the models highlight the potential for individual symptoms of mild severity to accrue into substantial symptom load. These observations may have important implications for patients, because mild symptoms can easily be overlooked.

In surveys of patients with cancer and disturbed sleep, between 38% and 85% did not discuss the issue with clinicians; often because it seemed unimportant relative to the cancer itself.[93,232] Mild symptoms may also go unrecognized in clinical assessments. For example, among 8,265 adults with cancer, 70% did not meet diagnostic thresholds for anxiety or depression,[233] yet in the present study, at least half of the participants reported some level of sadness (50%) or distress (55%). In our sample, distress (rated by patients) stands out as the most universal and strongest (indicated by standardized regression coefficients) correlate of SDS. Notably, however, clinician-rated psychological distress was not a correlate, nor was history of diagnosed depression (personal or family). Evaluating symptoms independently and in terms of diagnostic thresholds may fail to unmask additive effects that may manifest from mild symptoms occurring contemporaneously.

Unfortunately, symptom multiplicity is a hallmark of cancer and its treatment. Fatigue, pain, and insomnia are often experienced concurrently in oncology, and it has been proposed that these symptoms (along with depression and cognitive difficulty, in some models)[234] represent a syndrome with a common underlying mechanism.[235] In the present study, however, these associations were not consistent across groups; fatigue did not correlate with SDS in lung or prostate cancer, and although pain was a correlate overall, in sub-group analysis it correlated with SDS only in colorectal cancer. These findings signal the possibility of additional clinically important interactions between sleep and other symptoms, some of which may have more relevance for certain patient populations than the fatigue-pain-insomnia relationship. Uncovering such associations may help in clarifying pathophysiologic mechanisms and developing more targeted interventions for cancer symptom management.

Distress

Among the eighteen symptoms evaluated, distress was the strongest and only universal correlate of sleep disturbance. There is growing evidence that distress and disrupted sleep are related, perhaps reciprocally.[236-240] Considerable variation in the operationalization of *distress*, however, complicates interpretation. The National Comprehensive Cancer Network (NCCN) describes 'distress' as encompassing a range, "from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis."[241] In other oncology literature, 'distress' is a more global term, including physical dimensions as well (also termed ‘symptom distress’).[242] Because the NCCN has identified ‘emotional’ as a stigmatizing term, along with ‘psychological’ and ‘psychiatric’,[241] terms such as ‘bother’ and ‘upset’ are used in some surveys to distinguish emotional distress from physical distress, but participants may have different interpretations for these terms.[242] Furthermore, with only a single measure, it is impossible to make distinctions between, for example, participants with financial worries and those with existential crises. In this study, therefore, the strong correlation observed between distress and sleep disturbance may represent a number of diverse relationships and processes. A clear understanding of sleep-distress interactions would allow for more focused and effective interventions, but this requires an increase in the number and precision of measures used to characterize both sleep disturbance and distress. A few recent studies have employed polysomnography to measure sleep objectively,[236,238,239] but measures for stress are limited and simulated stressors may have little bearing on real-life experiences. Longitudinal studies in oncology settings would likely yield a wealth of insights.

Non-symptom correlates of sleep disturbance

Five non-symptom factors correlated with SDS: age (overall and breast cancer), clinical status (colorectal cancer), hormone therapy (breast cancer), benzodiazepine use (overall), and anticonvulsant use for pain (prostate cancer).

Age. In the general population, risk of sleep disturbance increases with age,[31] yet we found the opposite trend: SDS decreased with age in breast cancer participants and overall (although the overall result was likely driven by the large breast cancer cohort). Other studies of cancer symptoms have also observed inverse relationships between age and sleep disturbance.[80,89,243] Suggested explanations include psychosocial and treatment factors pertinent to younger people, who generally have better baseline health and functional status and may have more demanding social roles. These patients may receive more aggressive treatments with greater toxicities[81] and/or experience decrements in health and function more profoundly.[244] Younger patients may also have greater unmet needs for psychosocial support, relative to retirees no longer caring for children.[89,245] Similarly, in studies not specific to cancer it has been suggested that older adults may be more tolerant of sleep disturbance because they experience less 'role impairment' from daytime effects of sleep loss.[27,246] Several psychosocial, clinical, and treatment variables were evaluated in this study, but symptoms – especially distress – were generally better correlates of SDS. After excluding symptoms, however, recent employment change correlated with increased SDS in every group. Notably, breast cancer participants were distinct from other groups by being the youngest and almost all female. It may be worth investigating whether younger females experience unique psychosocial stressors (e.g., childcare, eldercare) not measured in this study.

Clinical status. Among participants with colorectal cancer, those in remission (disappearance) reported worse SDS than those with stable disease. A similar, but non-significant, trend was seen for partial response and progression. The relative association is small (standardized regression coefficient = -0.096), but nonetheless counterintuitive. Given the physical and psychological distress associated with cancer and its treatment, one might expect improved sleep after remission. There is some evidence, however, that colorectal cancer survivors have worse health-related quality of life than survivors of other solid tumor cancers.[247-249] In particular, patients with ileostomy/colostomy report disrupted sleep from leakage, ballooning, and anxiety about such events.[250,251] We were unable to control for this variable, however, as it was not measured in the original SOAPP study.

Cancer treatment. The only cancer treatment correlated with SDS was hormone therapy for breast cancer. Hormone blockade is common for treating breast and prostate cancer. Although therapeutic targets differ by site (prostate: testosterone; breast: estrogen and/or progesterone), common side effects in both cases include hot flashes and night sweats, which can disrupt sleep. In our sample, hormone therapy was more common in prostate cancer, but correlated with SDS only in breast cancer. Prevalence estimates for hot flashes are varied, but risk does not appear markedly greater for women (51%-81%) than men (69%-76%).[252] It may be, however, that hot flashes in women are more severe or less well controlled (e.g., citalopram is an effective remedy, but contraindicated in women taking tamoxifen). Comparative evaluations of hot flashes in both men and women may yield new insights for prevention and treatment.

Medications. Two medication classes correlated with SDS in our study: benzodiazepine receptors agonists (BzRAs, e.g. zolpidem, zaleplon), and anticonvulsants used for pain (e.g. pregabalin, gabapentin). In the whole cohort, BzRA use correlated with a 0.7-point increase in SDS severity. Since BzRAs are indicated for insomnia, correlation between sleep disturbance and BzRA use is unsurprising. Ideally, however, BzRA users would report decreased symptom severity, relative to non-users. It may be that BzRA users comprise the worst cases whose scores would be dramatically higher without treatment. Alternatively, our results may be confounded by unmeasured use of over-the-counter or non-pharmacological remedies. Notably, however, we did observe a substantial 1.3-point SDS decrease in men with prostate cancer using anticonvulsants for pain. This result is unlikely related to severity of sleep disturbance (higher in breast and lung cancer, lower in colorectal cancer) or prevalence of anticonvulsant use (no difference across groups), but may be related to pain control (lowest reported severity in prostate cancer). Although SOAPP data do not identify specific anticonvulsants, gabapentin and pregabalin have the best evidence for cancer-related neuropathy.[253] Furthermore, these anticonvulsants are sedating and appear to increase slow-wave (SWS) and rapid eye-movement (REM) sleep[254] (considered vital to physical and mental restoration, respectively),[255] whereas BzRAs may inhibit or fragment these sleep stages.[256] Our findings of positive (for BzRAs) or null (for BZDs) correlations between SDS and hypnotics call into question whether these standard insomnia treatments are the best choice for people with cancer. The effectiveness of sedative-hypnotics in this setting has not been established in clinical trials, and more research – including evaluation of drugs that could target multiple symptoms – is needed.

Comparisons across cancer types

The key similarity among cancer-specific groups was the importance of symptoms as correlates of sleep disturbance. Distress was the only universal correlate, and its largest relative effect was seen in prostate and lung cancer (standardized regression coefficients: 0.373 and 0.347, respectively). Fatigue, pain, drowsiness, and cognitive problems appeared in multiple models, but other correlates were shared. It should be noted, however, that groups were unmatched on several sample characteristics [**Table 3.3**] and in size. Commonalities may have gone undetected due to loss of power in smaller groups (e.g., lung and prostate cancer).

Strengths and limitations

To our knowledge, this is the largest and most comprehensive epidemiological study of sleep disturbance in oncology that allows for comparisons across different cancer types, but several limitations must be considered. As a secondary analysis, selection bias cannot be ruled out and subgroups were not matched in size or demographic characteristics. Furthermore, generalizability may be limited to ambulatory patients with solid tumors treated by an oncology group in the Eastern United States. The single subjective sleep disturbance measure likely captured a wide variety of sleep disturbances (e.g., restless limbs, apnea, delayed onset, early waking, feeling unrestored), but did not permit distinctions among them. Selection of independent variables was based on a causal model, but the cross-sectional design and unknown duration of sleep disturbance (and certain correlate variables) prohibit causal inference. Finally, use of non-prescription medications, supplements, alcohol was not accounted for and could confound our results.

Conclusions

We aimed to identify, from a large set of variables, the most important correlates of sleep disturbance in persons with cancer. Based on the 3P (predisposing, precipitating, perpetuating) model of insomnia, we evaluated demographics, clinical characteristics, cancer treatments, palliative medications, and cancer symptoms. Although average symptom severity scores were generally mild (mostly ≤ 3 on a 0 to 10 scale), cancer symptoms dominated the models. Comparing across cancer-specific subgroups, distress was the only universal correlate, but cognitive difficulty, drowsiness, and fatigue were also common. Benzodiazepine receptor agonists, specifically indicated for insomnia, correlated with a small increase in SDS overall (no associations were found with other hypnotics), while use of anticonvulsants for pain correlated with a relatively large SDS decrease in prostate cancer. The clinical and research implications of these findings are: 1) Even when individual symptoms are mild, patients with multiple symptoms may experience substantially worsened sleep. Research aimed at identifying causal pathways and interactions may help clinicians to better manage overall symptom burden. 2) Standard pharmacotherapy for insomnia may not benefit persons with cancer as much as treatments that target multiple symptoms. Hypnotics are not well studied in this population and more research is needed.

3.2 Section II: Manuscript 2

Hypnotic Use Prevalence and Correlates in Solid Tumor Cancers

Introduction

For well over a decade, oncology clinicians and researchers have recognized sleep disturbance to be an important problem for patients.[80,81,93] It is one of the most common and severe cancer symptoms reported,[82,90,110] and can reduce health-related quality of life,[87,91,111] exacerbate other cancer symptoms[81,137] and worsen prognoses.[88,89] Yet to date, there is little evidence to guide treatment in this setting.[156,164]

Sleep disturbance may be treated both pharmacologically and non-pharmacologically. The most studied non-pharmacologic option is cognitive behavioral therapy for insomnia (CBT-I) to correct beliefs and behaviors that interfere with sleep.[3] CBT-I is free of adverse effects, and benefits can be long-lasting, but it often takes time to see results.[3] In persons with cancer, CBT-I has shown promise for improving insomnia.[121-124] When acute relief is needed, however, or when sleep disturbance is not primarily due to beliefs and behaviors, pharmacologic insomnia treatments (*hypnotics*) may be preferred.

Historically, hypnotic use has been common in oncology settings. Among 1,984 Canadians with cancer surveyed in 2004, 41% received prescriptions for hypnotics, 37% had used hypnotics at some time since diagnosis, and 23% currently used hypnotics.[135] Similarly, in the late 1990s, 26% of 909 Israeli oncology patients reported hypnotic use in the previous week.[136] In the United States (US), estimates of hypnotic use in oncology exceeded 50% in the 1970s and 1980s, with benzodiazepines and antihistamines being prescribed most frequently.[137,138] These figures far outpace use of hypnotics in the general population, which is estimated at about 3-4%.[145,257]

More recent patterns of hypnotic use in US oncology patients are not well studied. This is noteworthy because the current standard-of-care drugs for insomnia, benzodiazepine receptor agonists (BzRAs), were introduced in the 1990s. Zolpidem

(Ambien®, Sanofi) first entered the US market in 1992, followed by zaleplon (Sonata®, Pfizer) in 1999, and eszopiclone (Lunesta®, Sunovion Pharmaceuticals) in 2004.[143] With the hypnotic efficacy of benzodiazepines, but fewer side effects, BzRAs quickly became preferred for insomnia, accounting for about 40% of hypnotic use nationwide by 2010.[145] In the US oncology setting, however, recent knowledge of hypnotic use is, to date, limited to a few small studies [**Table 3.6**]. Current data on which drugs are being prescribed, how often, and to whom, is a vital first step in assessing, and improving, the treatment of sleep disturbance in persons with cancer.

This study aims to quantify hypnotic use in a large diverse sample of persons with cancer, and to identify – from a large number of demographic, clinical, treatment, and clinician assessment variables – the significant correlates of hypnotic use by cancer patients overall, as well as for specific types of cancer.

Table 3.6 Summary of recent studies quantifying hypnotic us in US oncology patients

Study	**Time Period**	**Site**	**Sample**	**Findings**
Koopman et. al. (2002) [141] Secondary analysis	January 1991 to December 1996	Multiple sites. San Francisco Bay Area, CA	97 women with metastatic or locally recurrent breast cancer	37% reported sleeping pill use within last 30 days
Guo et. al. (2007) [140] Medical record review	September 2002, through October 2003	Large tertiary care cancer center. Houston, TX	96 adults undergoing acute inpatient rehabilitation	24% were given hypnotics upon discharge
Moore at. al. (2011)[258]	April 2003 through May 2006	Multiple sites. Midwestern US	219 women receiving chemotherapy for breast cancer	20% used sleep aids prior to chemotherapy; use decreased over time (12-18%)
Costantini C, Ale-Ali A, Helsten T. (2011) [142] Medical record review	April 2008 through March 2010	University of California. San Diego, CA	124 women receiving chemotherapy for breast cancer	32% received hypnotic prescriptions during chemotherapy; benzodiazepines comprised 39% of prescriptions

Methods

This was a secondary analysis of the Symptom Outcomes and Practice Patterns (SOAPP) study conducted from March 3, 2006 to May 19, 2008 in about 40 clinics and academic centers located primarily in the Eastern United States. This study is a secondary analysis of the SOAPP data, and the support of the ECOG-ACRIN* Cancer Research Group and SOAPP Study Steering Committee in accessing these data is acknowledged. The results and conclusions in this paper are those of the authors and do not indicate concurrence by ECOG-ACRIN or the SOAPP Study Steering Committee.

Participants

Outpatients at least 18 years of age at any stage of care for invasive breast, lung, prostate, or colorectal cancer were eligible to participate; respondents with inadequate cognitive function (assessed by a study screener) were excluded.[171] Clinicians provided clinical data, including medication use, and evaluated patient quality of life in multiple health-related domains. Patients provided demographic data.

Study variables

Hypnotic use. In the original SOAPP study, clinicians identified patient medications by category. The 'hypnotics' category comprised benzodiazepines (BZDs), and non-BZDs. Examples listed for non-benzodiazepine hypnotics were zolpidem (a BzRA) and chloral hydrate. Chloral hydrate was not widely used in oncology studies immediately preceding the introduction of BzRAs, and is not commonly used in recent studies of the general population. Therefore, this study assumes that 'non-benzodiazepine hypnotics' represent mainly BzRAs. BZDs were

* A merger of the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN)

further partitioned into long- or intermediate-acting (e.g, clonazepam, clorazepate, flurazepam, lorazepam) and short-acting (e.g., oxazepam, triazolam, alprazolam) because short-acting BZDs are sometimes used for anxiety, independently of sleep disturbance. We note, however, that clinicians may have assigned BZDs differently, as categorization by duration of action is not consistent in the literature.

Correlate variables. Many demographic, clinical, treatment, and clinician assessment variables were measured in the original SOAPP study. For this analysis, we identified the following four categories of potential hypnotic use correlates:

1. *Disturbed sleep* was rated by patients at its worst in the last 24 hours (scaled from 0='Not present' to 10='As bad as you can imagine') as part of a survey adapted from the MD Anderson Symptom Inventory (MDASI).[224] To aid interpretation, we defined the following sleep disturbance groups: None (0), Mild (1-4), Moderate (5-6), and Severe (7-10). Although the literature is not conclusive, cut-points of 5 and 7 are often identified as clinically meaningful thresholds for cancer symptom assessments that use 0 to 10 scales (e.g., Edmonton Symptom Assessment Scale, Brief Fatigue Inventory, Brief Pain Inventory).[179,180,182]
2. *Sleep disturbance risk factors* may be categorized by the '3P' model of insomnia as *predisposing* (e.g., physiological, psychological, or socioeconomic factors that increase vulnerability to sleep disruption), *precipitating* (e.g., life events that trigger acute insomnia), and/or *perpetuating* (e.g., factors that inhibit adaptation and return to normal sleeping patterns).[183] Established predisposing factors for insomnia in the general population include older age, female sex, history of mental illness, and low socioeconomic status. In the context of cancer, sleep may be disrupted by clinical factors (e.g., disease stage, functional status) and treatments (e.g., chemotherapy, hormone therapy). **Table 3.7** lists demographic, clinical, and treatment variables included in saturated models.

Table 3.7 Potential mediators of sleep disturbance included in models for hypnotic use

Demographic variables	**Clinical variables**	**Treatment variables**
Age	Primary site	Prior radiotherapy
Sex	*Breast*	Current radiotherapy
Male	*Colorectal*	Prior number of regimens
Female	*Prostate*	*None*
Race	*Lung*	*1*
White	Months since diagnosis	*2*
Black	Cancer stage	*3 or more*
*Other**	*No evidence of disease*	Current chemotherapy
Ethnicity	*Local/regional*	*None*
Hispanic	*Metastatic*	*Systemic single*
Non-Hispanic	*Local/regional/metastatic*	*Systemic multi*
Employment status	Cancer status	*Nonsystemic/Noncytotoxic*
Part-time	*Disappearance*	Current immunotherapy
Full-time	*Partial response*	Current hormone therapy
Not employed	*Stable*	Current treatment stage
Employment change in last 4 weeks	*Progression*	*None*
Driving in last 4 weeks	ECOG performance status	*Adjuvant*
History of depression	*0*	*Non-metastatic*
Family history of depression	*1*	*Metastatic*
	2	Attending support group
	3 & 4	Attending counseling
	Cognitive function	
	No impairment	
	Partial impairment	
	Pain history	
	None currently	
	< 48 hours	
	< 1 month	
	> 1 month	
	> 6 months	
	Pain mechanism	
	None	
	Nociceptive	
	Neuropathic	
	Psychological distress	

* Excluded due to small cell sizes

Table 3.8 Medications commonly used in cancer symptom management with known or potential effects on sleep.

Drug class	Examples	Use in oncology	General effect
5-HT3 antagonists	Ondansetron, granisetron, dolasetron	Nausea & vomiting	Sedating
Anticonvulsants	Gabapentin, pregabalin	Nerve pain	Sedating
Antidepressants	Doxepin*, trazodone, mirtazapine	Nerve pain	Sedating
Antihistamines	Diphenhydramine*†, doxylamine*†, chlorpheniramine†, promethazine, hydroxyzine	Hypersensitivity reaction	Sedating
Antipsychotics	Olanzapine, quetiapine	*Delirium – Not studied*	Sedating
Cannabinoids	Dronabinol	*Pain, nausea & vomiting – Not studied*	Sedating
Corticosteroids	Dexamethasone, prednisolone	Nausea & vomiting, pain, immunosuppression, others	Excitatory
Miscellaneous anxiolytics & antidepressants	Buspirone, hydroxyzine, trazodone, mirtazapine, quetiapine, olanzapine	Anxiety, depression, insomnia, delirium	Sedating
Neurokinin-1 inhibitors	Aprepitant	Nausea & vomiting	Sedating
Opioid analgesics	Morphine, fentanyl	Pain	Sedating
Other antiemetics	Promethazine, metoclopramide	Nausea & vomiting	Sedating
Tricyclic antidepressants	Amitriptyline, nortriptyline,	Depression, anxiety, nerve pain	Sedating

* Approved by United States Food & Drug Administration for treatment of insomnia.
† Over-the-counter (nonprescription) medications.

3. *Medications used to control symptoms* often have effects on sleep [**Table 3.8**]. Sedating drugs could negatively correlate with hypnotic use either by incidentally obviating their need or due to being deliberately prescribed for this indication. Alternatively, increased hypnotic use might be observed in participants using corticosteroids, which have detrimental effects on sleep.
4. *Clinician assessments of patient experiences*. In the SOAPP study, clinicians assessed patients' health-related quality of life in two ways. First, by identifying from a list of symptoms (e.g., pain, fatigue, cough) and lifestyle problems (e.g., spiritual problems, financial problems), the top three[3] areas causing difficulty for their patients. Second, by rating (from 0='Not at all' to 4='Extremely') the degree to which their patients were bothered by difficulties related to: cancer, cancer treatments, comorbidities, side effects from symptom care medications, and weight gain/loss. We also evaluated type of clinician (attending physician, resident or fellow, advanced practice nurse or nurse practitioner, physician assistant, other) as a potential correlate of hypnotic use.

Statistical analyses

Software. Statistical analyses were conducted using the following software: Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.), SAS (SAS Institute. 2015. The SAS system for Windows. Release 9.4. SAS Institute, Cary, NC.), and IVEware (University of Michigan. 2002. IVEware: Imputation and Variance Estimation Software).

Missing data analysis. The percentage of missing values was low (<4%) for most independent variables, except ethnicity (7.18%), current hormone therapy (16.25%), and current immunotherapy (18.35%), none of which were included in final models. With a large number of variables, however, listwise deletion would reduce the sample by about 25%. Using SAS software and a callable routine built with IVEWare,

[3] This study evaluated only the top two-ranked areas; the third item was mostly missing.

values were multiply imputed (*m=5*) through sequential multiple regression by chained equations to accommodate heterogeneity of variable type and distribution.[201-203] Comparison of imputed datasets by analysis of variance (ANOVA) revealed no differences for any variables, except current hormone therapy (F=5.54 [1,13903], p=0.0186). Final regression analyses were, therefore, performed on a singly-imputed dataset, to facilitate additional analytic procedures, including regression diagnostics.

Statistical analyses. Starting with a saturated model [**Table 3.7**], we used binary logistic regression to identify correlates of hypnotic use. Models were reduced based on significance level for each correlation coefficient, and model fit was evaluated with Bayesian Information Criterion values. For each factor level, we estimated hypnotic use probabilities standardized to the total group (covariates controlled using weighted averages).[207,208] After modeling the total sample, cancer site-specific models were evaluated using the same methods. To mitigate Type I error risk from multiple analyses, we used a significance cutoff of $p<0.01$.

Results

Sample characteristics

Of 3,106 participants in the SOAPP study, 2,382 met the inclusion criteria. The sample was 71% female, 86% white, and mean age was 61 years (range, 23 to 93 years). A total of 62.8% reported at least some degree of sleep disturbance [score >0/10]; 26.3% rated their sleep disturbance as moderate to severe [score >=5/10].

Hypnotic use. Overall, 23.5% of participants used a BZD/BzRA hypnotic. Among those reporting any degree of sleep disturbance, 28.8% used a hypnotic. For moderate-to-severe sleep disturbance, 35.2% used hypnotics. Hypnotic users were, on average, slightly younger than non-users, and hypnotic use was more common in females, whites, non-Hispanics, participants with breast cancer, and those with stable disease [**Table 3.9**].

Table 3.9 Sample characteristics overall and dichotomized by hypnotic use

		TOTAL SAMPLE		No Hypnotic Use		Hypnotic Use		*F*	*p*
		Mean	***(SD)***	***Mean***	***(SD)***	***Mean***	***(SD)***		
	Age, years	**60.9**	**(12.2)**	61.7	(12.2)	58.3	(11.8)	*34.50*	*< 0.001**
		N	***(%)***	***N***	***(%)***	***N***	***(%)***		
TOTAL SAMPLE		***2382***	***(100.0)***	***1822***	***(76.5)***	***560***	***(23.5)***	X^2	***p***
Sleep disturbance severity	None [0]	**887**	**(37.2)**	757	(41.6)	130	(23.2)	*87.144*	*<0.001**
	Mild [1-4]	**870**	**(36.5)**	660	(36.2)	210	(37.5)		
	Moderate [5-6]	**306**	**(12.9)**	203	(11.1)	103	(18.4)		
	Severe [7-10]	**319**	**(13.4)**	202	(11.1)	117	(20.9)		
Sex	Male	**693**	**(29.1)**	566	(31.1)	127	(22.7)	*16.603*	*<0.001**
	Female	**1689**	**(70.9)**	1256	(68.9)	433	(77.3)		
Race	White	**2052**	**(86.1)**	1539	(84.5)	512	(91.4)	*18.745*	*<0.001**
	Black	**283**	**(11.9)**	246	(13.5)	38	(6.8)		
	Other	**47**	**(2.0)**	37	(2.0)	10	(1.8)		
Ethnicity	Hispanic	**187**	**(8.1)**	154	(8.5)	24	(4.3)	*10.755*	*0.001**
	Non-Hispanic	**2195**	**(91.9)**	1668	(91.6)	536	(95.7)		
Primary site	Breast	**1212**	**(50.9)**	914	(50.2)	298	(53.2)	*25.345*	*<0.001**
	Colorectal	**570**	**(23.9)**	444	(24.4)	126	(22.5)		
	Prostate	**237**	**(10.0)**	256	(14.1)	107	(19.1)		
	Lung	**363**	**(15.2)**	208	(11.4)	29	(5.2)		
Cancer status	Disappearance	**908**	**(38.1)**	758	(41.6)	151	(27.0)	*39.505*	*<0.001**
	Partial response	**122**	**(5.1)**	89	(4.9)	32	(5.7)		
	Stable	**1029**	**(43.2)**	736	(40.4)	291	(52.0)		
	Progression	**323**	**(13.6)**	239	(13.1)	86	(15.4)		
Clinician: sleep is a top HRQoL problem	No	**2120**	**(89.0)**	1629	(89.4)	491	(87.7)	*1.308*	*0.253*
	Yes	**262**	**(11.0)**	193	(10.6)	69	(12.32)		

HRQoL: health-related quality of life

The distribution of hypnotic use by class was fairly even: 31% long- or intermediate-acting BZDs, 41% short-acting BZDs, and 28% BzRAs [**Figure 3.1**]. We note that this distribution is subject to some uncertainty, because classification of BZDs by duration of action is not consistent in the literature. There were no differences in hypnotic class used on the basis of sleep disturbance severity, age, sex, race, ethnicity, primary site, or cancer status.

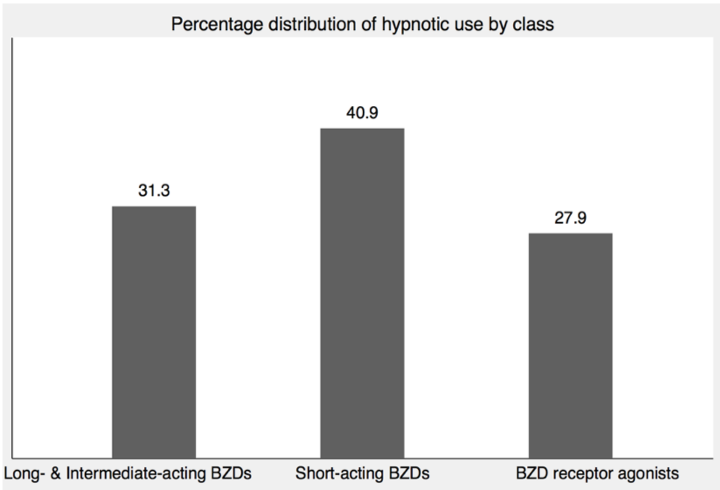


Figure 3.2 Distribution of hypnotic use by class. Examples of intermediate-/long-acting BZDs include: clonazepam, clorazepate, and flurazepam. Short-acting BZDs include oxazepam, triazolam, and alprazolam. BzRAs include zolpidem and zaleplon. Classification by duration of action is inconsistent for some BZDs (e.g., lorazepam, alprazolam).

Cancer site-specific groups. Primary cancer sites were: breast (51%), colorectal (24%), lung (15%), and prostate (10%). **Table 3.10** shows subsample characteristics for each cancer site. On average, breast cancer patients were youngest (57.6 ± 11.4 years), and prostate cancer patients were oldest (71.0 ± 9.5 years; $F[3,2378]=109.47$; $p<0.001$). No gender difference was detected between lung and colorectal cancer (evaluated separately from breast and prostate cancer). Groups differed by Hispanic/non-Hispanic ethnicity ($X^2[3]=23.96$; $p<0.001$), but not race. Cancer disappearance was most common for breast cancer, while lung and prostate cancer had higher frequencies of partial response, progression, and stable disease ($X^2[9]=308.43$; $p<0.001$).

Models for hypnotic use

Table 3.11 shows the best-fitting models for correlates of hypnotic use overall, and in each cancer-specific group. Along with regression coefficients, we report predicted probabilities and relative risk ratios.

Overall sample (N=2,382). The model for the total sample accounts for 12.6% of variance ($X^2(19)=388.52$; $p<0.001$; adjusted $R^2=0.126$; $BIC'=-240.779$). Correlates: race, history of depression, clinical status, opioids, corticosteroids, promethazine, neurokinin-1 inhibitors, miscellaneous anxiolytics/ antidepressants, metoclopramide, and clinician rating for patients' difficulty with cancer treatment.

Breast cancer (N=1,212). Model accounts for 15.1% of variance ($X^2(16)=256.75$; $p<0.001$; adjusted $R^2=0.151$; $BIC'=-143.147$). Correlates: race, history of depression, clinical status, promethazine, neurokinin-1 inhibitors, 5-HT3 antagonists, metoclopramide, and clinician rating for patients' difficulty with cancer treatment.

Colorectal cancer (N=570). Model accounts for 7.2% of variance ($X^2(6)=65.42$; $p<0.001$; adjusted $R^2=0.072$; $BIC'=-27.347$). Correlates: psychological distress, opioid use, corticosteroids, and promethazine.

Lung cancer (N=363). Model accounts for 7.8% of variance ($X^2(4)=50.34$; $p<0.001$; adjusted $R^2=0.078$; $BIC'=-26.759$). Correlates: race, history of depression, corticosteroids.

Prostate cancer (N=237). Model accounts for 10.4% of variance ($X^2(5)=34.26$; $p<0.001$; adjusted $R^2=0.104$; $BIC'=-6.924$). Correlates: promethazine, and clinician rating for patients' difficulty with cancer.

Table 3.10 Sample characteristics overall and for cancer-specific subgroups, including all significant correlates

		Total Sample		Breast Cancer		Colorectal Cancer		Lung Cancer		Prostate Cancer			
		N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**		
		2382	**(100.0)**	**1212**	**(50.9)**	**570**	**(24.0)**	**363**	**(15.2)**	**237**	**(10.0)**	**X^2 Test**	***p*-value**
Sleep disturbance severity score	*None* [0]	**887**	**(37.2)**	429	(35.4)	237	(41.6)	124	(34.2)	97	(40.9)	14.7	0.098
	Mild [1-4]	**870**	**(36.5)**	450	(37.1)	204	(35.8)	133	(36.6)	83	(35.0)		
	Moderate [5-6]	**306**	**(12.9)**	155	(12.8)	71	(12.5)	49	(13.5)	31	(13.1)		
	Severe [7-10]	**319**	**(13.4)**	178	(14.7)	58	(10.2)	57	(15.7)	26	(11.0)		
Sex	*Male*	**693**	**(29.1)**	3	(0.2)	293	(51.4)	160	(44.1)	237	(100.0)	1200	<0.001
	Female	**1689**	**(70.9)**	1209	(99.8)	277	(48.6)	203	(55.9)	0	(0.0)	4.77*	0.029*
Race	*White*	**2052**	**(86.2)**	1064	(87.8)	473	(83.0)	316	(87.1)	199	(84.0)	12.33	0.055
	Black	**283**	**(11.9)**	126	(10.4)	85	(14.9)	37	(10.2)	35	(14.8)		
	Other	**47**	**(2.0)**	22	(1.8)	12	(2.1)	10	(2.8)	3	(1.3)		
Ethnicity	*Hispanic*	**187**	**(7.9)**	83	(6.9)	65	(11.4)	13	(3.6)	26	(11.0)	23.96	<0.001
	Non-Hispanic	**2195**	**(92.2)**	1129	(93.2)	505	(88.6)	350	(96.4)	211	(89.0)		
History of depression	*No*	**187**	**(7.9)**	83	(6.9)	65	(11.4)	13	(3.6)	26	(11.0)	23.96	<0.001
	Yes	**2195**	**(92.2)**	1129	(93.2)	505	(88.6)	350	(96.4)	211	(89.0)		
Psychological distress	*No*	**1727**	**(72.5)**	887	(73.2)	417	(73.2)	240	(66.1)	183	(77.2)	10.47	0.015
	Yes	**655**	**(27.5)**	325	(26.8)	153	(26.8)	123	(33.9)	54	(22.8)		
Clinical status	*Disappearance*	**909**	**(38.2)**	642	(53.0)	194	(34.0)	42	(11.6)	31	(13.1)	308.43	<0.001
	Partial response	**120**	**(5.0)**	35	(2.9)	25	(4.4)	37	(10.2)	23	(9.7)		
	Stable	**1030**	**(43.2)**	420	(34.7)	256	(44.9)	221	(60.9)	133	(56.1)		
	Progression	**323**	**(13.6)**	115	(9.5)	95	(16.7)	63	(17.4)	50	(21.1)		
Pain treatment	*None*	**909**	**(38.2)**	642	(53.0)	194	(34.0)	42	(11.6)	31	(13.1)	308.43	<0.001
	Opioids	**120**	**(5.0)**	35	(2.9)	25	(4.4)	37	(10.2)	23	(9.7)		
	Non-opioids	**1030**	**(43.2)**	420	(34.7)	256	(44.9)	221	(60.9)	133	(56.1)		
	Combination	**323**	**(13.6)**	115	(9.5)	95	(16.7)	63	(17.4)	50	(21.1)		
Medication use	*Corticosteroids*	**459**	**(19.3)**	198	(16.3)	116	(20.4)	97	(26.7)	48	(20.3)	20.24	<0.001
	Promethazine	**392**	**(16.5)**	170	(14.0)	135	(23.7)	68	(18.7)	19	(8.0)	40.51	<0.001
	NK-1 inhibitors	**95**	**(3.99)**	67	(5.5)	16	(2.8)	12	(3.3)	0	0	19.87	<0.001
	Misc. Anxiolytics/ADs	**26**	**(1.1)**	14	(1.2)	10	(1.8)	2	(0.6)	0	0	5.96	0.113
	Metoclopramide	**55**	**(2.3)**	23	(1.9)	15	(2.6)	14	(3.9)	3	(1.3)	6.17	0.104
	5-HT3 antagonists	**426**	**(17.9)**	170	(14.0)	160	(40.3)	363	(2.7)	19	(8.0)	71.00	<0.001
Top quality of life problem	*Distress*	**262**	**(11.0)**	147	(12.1)	55	(9.7)	35	(9.6)	25	(10.6)	3.37	0.338
	Sleep	**262**	**(11.0)**	160	(13.2)	38	(6.7)	33	(9.1)	31	(13.1)	19.33	<0.001

* A secondary evaluation of sex and cancer site was performed for the colorectal and lung cancer groups only.

Table 3.11 Logistic regression model for correlates of hypnotic use in solid tumor cancers

Total sample (n=2382)	**N**	**(%)**	**Regression Coefficient**	**(SE)**	***p-value***	**Predicted Probability**	**(SE)**	**Relative Risk[a]**
Sleep Disturbance Severity								
None [0]	887	(37.2)	0.37	(0.13)		0.18	(0.01)	
Mild [1-4]	870	(36.5)	0.77	(0.17)	*0.567*	0.23	(0.01)	1.28
Moderate [5-6]	306	(12.9)	0.89	(0.17)	*0.001**	0.30	(0.02)	1.66
Severe [7-10]	319	(13.4)			*0.058*	0.32	(0.02)	1.77
Race								
White	2051	(86.1)	-0.90	(0.20)		0.25	(0.01)	
Black	284	(11.9)	-0.40	(0.40)	*<0.001**	0.13	(0.02)	0.54
Other	47	(2.0)			*0.286*	0.19	(0.05)	0.77
History of Depression								
No	1718	(72.1)	0.74	(0.11)		0.20	(0.01)	
Yes	664	(27.9)			*<0.001**	0.32	(0.02)	1.60
Clinical status								
Disappearance	909	(38.2)	0.14	(0.25)		0.20	(0.01)	
Partial response	121	(5.1)	0.41	(0.13)	*0.567*	0.22	(0.03)	1.10
Stable	1027	(43.1)	0.33	(0.17)	*0.001**	0.26	(0.01)	1.31
Progression	325	(13.6)			*0.058*	0.25	(0.02)	1.24
Pain treatment								
None	1460	(61.3)	0.44	(0.15)		0.22	(0.01)	
Opioids	362	(15.2)	0.18	(0.14)	*0.004**	0.28	(0.02)	1.32
Non-opioids	437	(18.4)	0.29	(0.23)	*0.167*	0.24	(0.02)	1.12
Combination	123	(5.2)			*0.247*	0.26	(0.03)	1.20
Corticosteroid use								
No	1923	(80.7)	0.65	(0.13)		0.21	(0.01)	
Yes	459	(19.3)			*<0.001**	0.32	(0.02)	1.50
Promethazine use								
No	1990	(83.5)	0.62	(0.13)		0.22	(0.01)	
Yes	392	(16.5)			*<0.001**	0.32	(0.02)	1.47
Neurokinin-1 inhibitor use								
No	2287	(96.0)	0.93	(0.24)		0.23	(0.01)	
Yes	95	(4.0)			*<0.001**	0.39	(0.05)	1.72
Miscellaneous anxiolytic/antidepressant use								
No	2356	(98.9)	1.32	(0.43)		0.23	(0.01)	
Yes	26	(1.1)	0.37	(0.13)	*0.003**	0.18	(0.01)	2.03
Metoclopramide use								
No	2327	(97.7)				0.23	(0.01)	
Yes	55	(2.3)	1.03	(0.31)	*0.001**	0.41	(0.06)	1.80
Clinician rating: cancer treatment bothers patient								
Not at all	592	(24.9)				0.16	(0.02)	
A little bit	879	(36.9)	0.51	(0.17)	*0.002**	0.23	(0.01)	1.43
Moderately	631	(26.5)	0.80	(0.17)	*<0.001**	0.27	(0.02)	1.73
Quite a bit	236	(9.9)	0.98	(0.21)	*<0.001**	0.30	(0.03)	1.92
Extremely	44	(1.9)	0.93	(0.38)	*0.014*	0.29	(0.06)	1.87

Likelihood ratio X^2 **(21)=388.52; p<0.001; adjusted pseudo (McFadden's)** R^2**=0.124;** ***BIC'*****=-225.256**

a. For each factor level, relative risk is calculated relative to the reference level.

Table 3.11a Logistic regression model for correlates of hypnotic use in breast cancer

a. Breast cancer (n=1212)	**N**	**(%)**	**Regression Coefficient**	**(SE)**	***p-value***	**Predicted Probability**	**(SE)**	**Relative Risk[a]**
Sleep Disturbance Severity								
None [0]	429	(35.4)				0.18	(0.02)	
Mild [1-4]	450	(37.1)	0.29	(0.19)	0.141	0.22	(0.02)	1.21
Moderate [5-6]	155	(12.8)	0.93	(0.24)	<0.001*	0.32	(0.03)	1.78
Severe [7-10]	178	(14.7)	1.27	(0.23)	<0.001*	0.38	(0.03)	2.13
Race								
White	1064	(87.8)				0.26	(0.01)	
Black	126	(10.4)	-1.09	(0.30)	<0.001*	0.13	(0.03)	0.49
Other	22	(1.8)	-0.18	(0.57)	0.701	0.23	(0.08)	0.90
History of Depression								
No	812	(67.0)				0.21	(0.01)	
Yes	400	(33.0)	0.62	(0.16)	<0.001*	0.31	(0.02)	1.44
Clinical status								
Disappearance	642	(69.8)				0.20	(0.02)	
Partial response	36	(2.97)	0.49	(0.41)	0.255	0.27	(0.06)	1.34
Stable	418	(34.5)	0.54	(0.17)	0.001*	0.28	(0.02)	1.38
Progression	116	(9.6)	0.65	(0.25)	0.015	0.30	(0.04)	1.48
Promethazine use								
No	1042	(76.3)				0.23	(0.01)	
Yes	170	(23.7)	0.66	(0.21)	0.002*	0.34	(0.03)	1.48
Neurokinin-1 inhibitor use								
No	1145	(94.5)				0.23	(0.01)	
Yes	67	(5.5)	1.21	(0.31)	<0.001*	0.44	(0.06)	1.91
5-HT3 antagonists								
No	1042	(76.3)				0.23	(0.01)	
Yes	170	(23.7)	0.71	(0.20)	0.001*	0.34	(0.03)	1.51
Metoclopramide use								
No	1189	(98.1)				0.24	(0.01)	
Yes	23	(1.9)	1.55	(0.51)	0.002*	0.52	(0.10)	2.15
Clinician: distress is a top HRQoL problem								
No	1065	(87.9)				0.23	(0.01)	
Yes	147	(12.1)	0.69	(0.21)	0.001*	0.34	(0.03)	1.48
Clinician rating: cancer treatment bothers patient								
Not at all	363	(30.0)				0.17	(0.02)	
A little bit	438	(36.1)	0.60	(0.22)	0.008*	0.25	(0.02)	1.48
Moderately	290	(23.9)	0.78	(0.23)	0.001*	0.27	(0.02)	1.65
Quite a bit	99	(8.2)	1.22	(0.30)	<0.001*	0.35	(0.04)	2.12
Extremely	22	(1.8)	0.86	(0.56)	0.115	0.29	(0.09)	1.73

Likelihood ratio $\boldsymbol{X^2(18)=254.23}$**; p<0.001; adjusted pseudo (McFadden's)** $\boldsymbol{R^2=0.145}$**;** ***BIC'*****=-126.433**

HRQoL: Health-related quality of life

Table 3.11b Logistic regression model for correlates of hypnotic use in colorectal cancer

b. Colorectal cancer (n=570)	**N**	**(%)**	**Regression Coefficient**	**(SE)**	***p-value***	**Predicted Probability**	**(SE)**	**Relative Risk[a]**
Psychological distress								
No	417	(73.2)				0.189	(0.02)	
Yes	153	(26.8)	0.74	(0.23)	0.001*	0.31	(0.04)	1.66
Pain treatment								
None	378	(66.3)				0.18	(0.02)	
Opioids	79	(13.9)	0.96	(0.29)	0.001*	0.34	(0.05)	1.92
Non-opioids	79	(13.9)	0.63	(0.30)	0.038	0.28	(0.05)	1.55
Combination	34	(6.0)	0.55	(0.43)	0.199	0.26	(0.07)	1.48
Corticosteroid use								
No	454	(80.0)				0.19	(0.02)	
Yes	116	(20.0)	0.96	(0.24)	<0.001*	0.35	(0.04)	1.90
Promethazine use								
No	435	(76.3)				0.19	(0.02)	
Yes	135	(21.7)	0.81	(0.23)	0.001*	0.32	(0.04)	1.74

Likelihood ratio **X^2(6)=65.42; p<0.001; adjusted pseudo (McFadden's)** ***R^2*****=0.072;** ***BIC'*****=-27.347**

Table 3.11c Logistic regression model for correlates of hypnotic use in lung cancer

c. Lung cancer (n=363)	**N**	**(%)**	**Regression Coefficient**	**(SE)**	***p-value***	**Predicted Probability**	**(SE)**	**Relative Risk[a]**
Race								
White	317	(87.3)				0.32	(0.03)	
Black	36	(9.9)	-1.54	(0.57)	0.007*	0.11	(0.05)	0.33
Other	10	(2.8)	-0.60	(0.76)	0.435	0.22	(0.11)	0.68
History of depression								
No	260	(73.8)				0.23	(0.03)	
Yes	95	(26.2)	1.21	(0.27)	<0.001*	0.48	(0.05)	2.06
Corticosteroid use								
No	266	(73.3)				0.23	(0.03)	
Yes	97	(26.7)	1.16	(0.26)	<0.001*	0.47	(0.05)	2.00

Likelihood ratio **X^2(6)=50.34; p<0.001; adjusted pseudo (McFadden's)** ***R^2*****=0.078;** ***BIC'*****=-26.795**

Table 3.11d Logistic regression model for correlates of hypnotic use in prostate cancer

d. Prostate cancer (n=237)	**N**	**(%)**	**Regression Coefficient**	**(SE)**	***p-value***	**Predicted Probability**	**(SE)**	**Relative Risk**[a]
Promethazine use								
No	218	(92.0)				0.10	(0.02)	
Yes	19	(8.0)	2.30	(0.60)	<0.001*	0.45	(0.12)	4.71
Clinician: how much is patient bothered by cancer								
Not at all	60	(25.3)				0.06	(0.03)	
A little bit	86	(36.3)	0.79	(0.72)	0.276	0.11	(0.03)	1.93
Moderately	53	(22.4)	1.30	(0.73)	0.073	0.16	(0.05)	2.86
Quite a bit	29	(12.2)	0.20	(0.92)	0.826	0.07	(0.04)	1.19
Extremely	9	(3.8)	3.60	(0.97)	<0.001*	0.62	(0.17)	10.84

Likelihood ratio $\boldsymbol{X^2(5)=34.26}$**; p<0.001; adjusted pseudo (McFadden's)** $\boldsymbol{R^2=0.104}$**;** ***BIC'*****=-6.924**

Correlates of hypnotic use

Sleep disturbance severity

Moderate sleep disturbance severity correlated with hypnotic use overall (p<0.001). This most likely represents the breast cancer group, however, which comprised half of the total sample and was the only subgroup in which sleep disturbance correlated with hypnotic use. Relative to participants with breast cancer reporting no sleep disturbance, hypnotic use was more likely for those with moderate (RR:1.78, p<0.001) or severe sleep disturbance (RR:2.13, p<0.001).

Demographic characteristics

Race correlated with hypnotic use overall and for breast and lung cancer. Overall, hypnotic use was 1.85 times more likely for whites than for black participants (RR for blacks: 0.54, p<0.001). In the breast cancer group, whites were twice as likely as blacks to use hypnotics (RR:0.49, p<0.001), and three times more likely in the lung cancer group

(RR:0.33, $p<0.001$). An *ad hoc* analysis found no association between race and whether clinicians identified sleep as a priority problem.

History of depression increased the likelihood of hypnotic use overall (RR: 1.60, $p<0.001$), as well as for breast (RR:1.44, $p<0.001$) and lung cancer (RR:2.06, $p<0.001$).

Clinical characteristics

Psychological distress, assessed by clinicians, correlated with hypnotic use in colorectal cancer only (RR: 1.66, $p=0.001$).

Clinical status was the only tested clinical variable correlated with hypnotic use overall. In the total sample, participants with stable disease were about 30% more likely to use hypnotics (RR: 1.31, $p<0.001$) than those in remission (disappearance). This likely reflects the group with breast cancer, in which stable disease similarly correlated with hypnotic use (RR: 1.38, $p<0.001$).

Treatment characteristics

No associations were found with clinician type, support group, counseling, any cancer-specific therapies (chemotherapy, radiotherapy, immunotherapy, hormone therapy), treatment stage, or prior number of regimens.

Supportive medications

Opioid analgesic use correlated with a 30% increase in hypnotic use, relative to no pain medication use, in the overall sample (RR: 1.32, $p=0.004$). For participants with colorectal cancer, opioid use nearly doubled the likelihood of hypnotic use (RR: 1.92, $p=0.001$).

Among the other evaluated symptom control medications with known effects on sleep, we found the following:

- *Corticosteroids,* used widely in oncology for antiemesis and immunosuppression, among other purposes, have excitatory central nervous system effects that can disrupt sleep.[105] Corticosteroid users were 50% more likely to use hypnotics overall (RR: 1.5, p<0.001), and twice as likely in the colorectal (RR: 1.9, p<0.001) and lung cancer (RR:2.0, p<0.001) groups. Despite increased hypnotic use by lung cancer participants using corticosteroids, *post hoc* analysis revealed this to be the only group in which corticosteroid use correlated with sleep disturbance ($X^2(3)=14.46$; p=0.002).
- *Promethazine,* a strongly sedating antiemetic/antihistamine, appeared in nearly every model. Likelihood of hypnotic use for promethazine users was 50% higher overall (RR: 1.47, p<0.001) and for breast cancer (RR:1.48, p=0.002). Larger increases were seen in colorectal (RR: 1.74, p<=.001), and prostate cancer (RR: 4.71, p<0.001).
- *5-HT3 antagonists* are antiemetics that may have beneficial effects on rapid eye movement (REM) sleep.[259] They correlated with hypnotic use in breast cancer only (RR: 1.51, p=0.001).
- *Neurokinin-1 inhibitors* are antiemetics that may improve improve sleep maintenance and prolong REM sleep with minimal sedation.[260] They correlated with hypnotic use overall (RR: 1.72, p<0.001), and for breast cancer (RR: 1.91, p<0.001), but were not evaluated in any other group due to small cell sizes.
- *Metoclopramide*, an antiemetic that can cause drowsiness,[261] correlated with hypnotic use overall (RR: 1.80, p=0.001), and for breast cancer (RR: 2.15, p=0.002), but was not evaluated in any other group due to small cell sizes.

- *Miscellaneous anxiolytics / antidepressants* were undefined, but those not otherwise explicitly listed in the SOAPP survey include hydroxyzine, buspirone, mirtazapine, trazodone, quietiapine, and olanzapine, all of which are sedating. Hypnotic use increased overall (RR: 2.03, p=0.003); cancer-specific groups were not evaluated due to small cell sizes.

Clinician ratings

Top health-related quality of life problems. From more than 20 symptom and health-related quality of life (HRQoL) items, clinicians were asked to identify the top three that most affected their patients' HRQoL. We evaluated the top two items, as the third was missing for most patients. The five most frequently identified problems were fatigue (42%), pain (29%), sleep (11%), distress (11%), and neuropathy (11%).

- *Sleep*. Notably, hypnotic use was not higher among participants for whom clinicians identified sleep as a top HRQoL issue. This raises the question of whether sleep disturbance is untreated due to lack of recognition. To explore this, we conducted a *post-hoc* chi-squared test and found agreement (significant association) between patients reporting sleep disturbance and clinicians identifying sleep as a priority problem ($X^2(3)=98.09$; $p<0.001$). This finding suggests that clinicians successfully recognized their patients sleep concerns, but did not prescribe a hypnotic for other reasons.
- *Distress* was the only top-ranked HRQoL problem correlated with hypnotic use, and only for participants with breast cancer (RR: 1.48, p=0.001). *Post-hoc* chi-squared analysis found agreement between patients reporting distress and clinicians identifying distress as a priority problem ($X^2(10)=32.19$; $p<0.001$), and identifying psychological distress in the clinical assessment ($X^2(10)=133.03$; $p<0.001$).

Patient's level of bother. Clinicians also rated the extent to which their patients were bothered by difficulties related to: cancer, cancer treatments, comorbidities, side effects from symptom care medications, and weight gain/loss. Ratings were scaled from 0='not at all' to 5='extremely'. Only two of these items correlated with hypnotic use: cancer and cancer treatment.

- *Cancer treatment*. Overall, probability of hypnotic use was higher for those rated to be bothered 'a little bit' (RR: 1.43, p=0.002), 'moderately' (RR: 1.73, p<0.001), or 'quite a bit' (RR: 1.92, p<0.001). The pattern was similar for breast cancer participants; 'a little bit' (RR: 1.48, p=0.008), 'moderately' (RR: 1.65, p=0.001), or 'quite a bit' (RR: 2.12, p<0.001).
- *Cancer*. In the prostate cancer group, those rated to be 'extremely' bothered by cancer were 10 times more likely to use hypnotics (RR: 10.84, p<0.001), but this result must be interpreted cautiously in light of the small cell size (n=9).

Discussion

To our knowledge, this is the first large US study of hypnotic use in a diverse sample of ambulatory cancer patients since benzodiazepine receptor agonists (BzRAs) became the standard of care, about a decade ago.

Prevalence of hypnotic use

The hypnotics we studied were benzodiazepines (BZDs) and benzodiazepine receptor agonists (BzRAs). Although their mechanism of action is the same, BZDs have more widespread effects throughout the central nervous system, and therefore more uses, but also more side effects than BzRAs.[262] In our sample of 2,382 participants, 24% used a

BZD or BzRA hypnotic; this is considerably higher than the general population estimate of 1.6%,[145] but well below the prevalence of sleep disturbance (62.8%). More importantly, BZD use outpaced BzRA use. In national estimates, BzRAs are preferred over BZDs by more than two to one.[145] In our sample, the ratio was inverted. Reliance on short-acting BZDs may be attributable, in part, to their role in treating anxiety and reducing anticipatory nausea and vomiting.[263] Use of a longer-acting BZD is a concern, however, in persons with cancer, not only because of the additional side-effects, but also because next-day residual effects can exacerbate fatigue and cognitive difficulties.[126]

Correlates of hypnotic use

The proportion of variance explained by our models was small (7-15%), but we did find some noteworthy relationships that warrant further investigation.

Sleep disturbance. A key finding in our study was the inconsistency with which sleep disturbance, as perceived by clinicians as well as by patients, correlated with hypnotic use. Our findings raise two issues. First, a significant correlation between sleep disturbance severity and hypnotic use, as seen in participants with breast cancer, may indicate treatment failure. Effective therapy should correlate with reduced symptom severity. A possible explanation is nonadherence with prescribed hypnotics, but we expect this would be less likely as symptom severity increases. Nonetheless, the effects of hypnotics in persons with cancer are not well studied. More research is needed to confirm their usefulness in this population and identify optimal regimens. The second issue is the high prevalence of sleep disturbance and relatively lower rate of hypnotic use, suggesting patients may be undertreated. Especially troubling was our finding that, even though clinicians often correctly identified when sleep was a priority problem for their patients, this was uncorrelated with hypnotic use. Clinicians tend to underestimate symptom severity, or altogether miss symptoms that are mild or subjective in nature,[264] which may explain this finding. Also, other drug classes (e.g., antidepressants, antipsychotics) not classified as hypnotics in this study may have been prescribed as sleep aids. We also note that prescriptions for hypnotics may more likely come from primary care physicians.[265] The American Society of Clinical Oncology (ASCO) recommends, however, that symptom management be integral to all stages of oncology care.[266] Little is known about prescriber knowledge of and attitudes toward hypnotic use in oncology, but general practitioners surveyed in the United Kingdom mostly endorsed negative attitudes toward BZD/BzRA hypnotics,[267] In the US, 90% of general practitioners surveyed in Ohio (n=580) rated their knowledge of sleep disorders as fair to poor,[268] and a 2005 survey found that sleep medicine comprised less than 2% of the content of medical textbooks. If practitioner beliefs and knowledge are barriers to treatment of sleep disturbance in oncology, then efforts should be made to improve awareness, but more research is needed to make this determination.

Racial disparity. Another important finding was racial disparity in hypnotic use. Sleep disturbance severity did not differ on the basis of race, nor did clinician ranking of sleep as a priority, yet white participants were about twice as likely to use hypnotics as blacks, overall and in the breast cancer group, and three times more likely in the lung cancer group. This finding is consistent with some limited research on hypnotic use,[269,270] and parallels well-documented disparities in pain treatment.[271-273] Troublingly, a review of pain management in emergency departments found that disparity was most frequent for pain that could not be objectively confirmed (e.g., headache, back pain, abdominal pain).[274] Given the subjective nature of sleep disturbance, a similar discounting of patient reports by clinicians may contribute to hypnotic use disparity. Conversely, prescribing of hypnotics may be influenced by patient requests, as observed among practitioners in German nursing homes.[275] Several studies have found that blacks are less likely than whites to believe that psychotropic medications (e.g., antidepressants, anxiolytics) are beneficial, more likely to have concerns about risks (e.g. addiction, impairment), and less likely to request or adhere to prescriptions.[276-279] Notably, however, in a sample of patients already experienced with psychotropic treatments, no such difference in beliefs was found.[280] There is evidence that lack of healthcare knowledge contributes to delayed help-seeking for cancer alarm symptoms (e.g., pain, palpable masses), leading to delays in cancer diagnosis for black patients.[281,282] If the same applies to help-seeking for symptom management, then interventions that build patients' awareness of the availability and efficacy of treatments may help to improve treatment equality. Racial disparity in hypnotic use is doubtless as multifaceted an issue as disparity in pain management, but is less well-studied. Much more research is needed to identify contributing factors and develop successful interventions for eliminating inequalities in the treatment of sleep disturbance.

Corticosteroid use. Sleep disruption is a common side effect of corticosteroids, so concurrent use of hypnotics is expected. Findings in lung cancer participants, however, may point to greater unmet needs. Only for lung cancer participants was corticosteroid use associated with sleep disturbance, even though corticosteroid users in that group were twice as likely to use hypnotics. Due to inappropriate hormone production by tumors, a small proportion (<5%) of lung cancer patients develop hypercortisolism (Cushing's) syndrome, and as many as 50% may experience subclinical cortisol elevation.[283] Sleep disruptions are known to occur in Cushing's disease,[284,285] and likely occur, albeit to a lesser extent, even with smaller cortisol elevations. This might help to explain our findings and would suggest that extra measures may be needed to address sleep disturbance in patients with lung cancer.

Polypharmacy. Excluding corticosteroids, all other medications we evaluated are sedating to various degrees. These drugs are primarily indicated for pain, anxiety, depression, and nausea/vomiting, all of which can disrupt sleep, so it is unsurprising that their use also correlates with hypnotic use. There is concern, however, that polypharmacy with sedating drugs could increase fall risk, already heightened in this population.[286] Notably, promethazine – so sedating it can be used alone as a sleep aid[287] – correlated with BZD/BzRA hypnotic use in every model except lung cancer. Polypharmacy also increases the risk of drug interactions. Because of substantial medication burden, the risk of drug interactions is high in oncology.[288,289] Even among patients receiving supportive care only, one study found potential interactions in nearly one-third (31%) of cases.[290] Of particular concern are opioids, which correlated with a nearly two-fold increase in hypnotic use for participants with colorectal cancer. Although opioid analgesics can improve sleep maintenance for patients awakened by overnight pain,[291,292] they may disrupt sleep architecture.[293,294] More importantly, BZD use in conjunction with opioids can exacerbate opioid-induced respiratory depression, increasing the risk of fatal overdose.[295] Management of complex symptom burdens along with complex antineoplastic regimens can be improved by engaging oncology pharmacists to assess and optimize regimens.[289,296,297] A better base of evidence is also needed, however, including prospective trials to identify the safest, most cost-effective therapies.

Clinicians. Although there was no relationship between clinician-identified sleep disturbance and participant hypnotic use, clinician-identified distress was correlated. Participants with breast cancer were more likely to use hypnotics if their clinicians identified distress as a priority problem or indicated that their patient was bothered by difficulties related to cancer treatment. A remarkable 10-fold increase was correlated with for participants with prostate cancer deemed ‘extremely’ bothered by cancer itself, but this result may be spurious, given the small, uneven sample size. *Post hoc* analyses indicated agreement between clinicians’ assessments and patient-reported distress, but this was also true of sleep disturbance (yet clinician-identified sleep disturbance was uncorrelated with hypnotic use). The past decade has seen increased awareness of and emphasis on the psychosocial needs of persons with cancer.[298-301] The International Psycho-Oncology Society (IPOS) recently identified distress as the 6th Vital Sign,[302] and efforts have been made to identify optimal screening tools.[300] Clinicians have expressed reservations about incorporating such screening into practice, however, because of limited ability to provide (or refer patients to) treatment.[303] Distress management guidelines developed by the National Comprehensive Cancer Network (NCCN) may help to address those concerns,[241] and, consistent with growing evidence relating distress and disrupted sleep,[236-240] the guidelines include sleep disturbance as both a symptom and risk factor.[241] Notwithstanding the relationship with distress, sleep disturbance can have many other causes and manifestations, the NCCN offers no guidelines for managing sleep disturbance beyond a few recommendations in the distress management guidelines. This may explain why clinicians were more likely to prescribe sleep aids to recognizably distressed patients; in absence of sleep-specific guidance, clinicians may be inclined to address sleep disturbance under the rubric of distress, if at all. As more evidence becomes available, efforts should be made to develop oncology-specific guidelines for managing sleep disturbance and to educate oncology clinicians.

Strengths and limitations

This study benefitted from a large sample and many measured variables, which permitted assessment not only across the entire sample, but also between cancer-specific groups, using consistent measurement and analytic methods. Cancer-specific groups were not well matched in size and for some characteristics, however, and generalizability of our results may be limited to ambulatory cancer patients treated by an oncology group in the

Eastern United States. A major limitation was the imprecise identification and classification of drugs, thus our analyses were limited to BZD/BzRA hypnotics and we were unable to evaluate or control for use of other classes of drugs as sleep aids. We were also unable to determine whether medications prescribed were actually taken. As a secondary analysis of survey data, this study is subject to selection and recall bias. With these limitations, and the fact that models accounted for only small proportions of variance ($\leq 15\%$), it is difficult to draw firm conclusions, but our findings raise important questions and can serve as a starting point to building a much needed base of evidence.

Conclusions

We aimed to identify, from a large set of variables, correlates of BZD/BzRA hypnotic use in persons with solid tumors. While the prevalence of hypnotic use, especially BZDs, was high relative to the general population, it was low relative to the prevalence of sleep disturbance in the sample. There is little evidence documenting the effects of these drugs in persons with cancer, and, therefore, little guidance for their use. Prospective trials are needed to assess the safety and efficacy of hypnotics in this population. Several sedating medications correlated with concomitant hypnotic use, putting this population at increased risk of drug interactions, including fatal respiratory depression with opioid analgesia. Pharmacists can make important contributions to the palliative care team by optimizing medication regimens. Prescribing patterns for hypnotics raised several concerns that should be further investigated, including undertreatment, racial bias, patient help-seeking behavior, polypharmacy, prescribers' attitudes, and disagreement between patient reports and clinician assessments. We suggest that studies evaluating prescribing behaviors along with clinician assessments of the patient experience may prove enlightening.

3.3 Section III: Manuscript 3

Change in cancer-symptom burden and health-related quality of life associated with sleep disturbance and hypnotic use in solid tumor cancers.

Introduction

At least half of all people with cancer experience sleep disturbance, and about 25% report the problem as moderate to severe.[80,81,93] The frequently observed clustering of sleep disturbance with other cancer symptoms such as pain, depression, and fatigue,[118,120,304] suggests underlying pathophysiology that is shared, to some extent.[235] Correspondingly, there is evidence of bidirectional relationships; that is, while sleep disturbance can exacerbate other cancer symptoms, such as pain and fatigue, these symptoms can also disrupt sleep. Improved understanding of relationships among cancer symptoms can help clinicians to streamline therapies; targeting a common etiology would require fewer interventions to manage symptom burden than would treating each symptom individually.

Relationships of pain, depression, and fatigue with sleep disturbance are well documented in the literature, but these are also symptoms that are commonly evaluated.[169] With mounting evidence for the role of sleep in homeostatic systems (e.g., metabolism,[59,60] immune function[44-47]), it is reasonable to expect that relationships exist between sleep and other cancer symptoms that are less frequently measured (e.g., cognitive function, appetite loss).[169] If this is the case, then therapies that improve sleep may prove to be integral in managing the total symptom burden of cancer.

Unsurprisingly, hypnotic use is common in the oncology setting, with estimates ranging from 20% to 37%.[140-142,258] Hypnotics are not well studied in persons with cancer,[159] however, and guidelines for treatment of cancer-related insomnia are substantially limited by lack of evidence.[156,157] It should not be assumed that accepted treatments for insomnia in the general population are appropriate for people with cancer. The oncology setting presents additional sources of sleep disruption as well as increased potential for drug-drug and drug-disease interactions, which can result in overall worsened outcomes. For example, benzodiazepine receptor agonists (BzRAs), which are considered first-line therapy for insomnia, could worsen cancer-related fatigue by producing next-morning drowsiness, motor incoordination, and cognitive difficulties.[9,10]

This study seeks to address research gaps pertaining to sleep disturbance and its treatment in people with cancer, with two primary aims: 1. To evaluate differences in symptom burden and health-related quality of life between hypnotic users and non-users. 2. To evaluate how changes in sleep disturbance severity relate to changes in other cancer symptoms and to health-related quality of life.

Methods

Data collection

From March 3, 2006 to May 19, 2008 the Eastern Cooperative Oncology Group (ECOG) conducted the Symptom Outcomes and Practice Patterns (SOAPP, also known as E2Z02) study in about 40 clinics and academic centers located primarily in the Eastern United States. Participants rated the severity of nineteen symptoms at the first visit, and at a second visit approximately 28 days later.[171] This study is a secondary analysis of the SOAPP data, and the support of the ECOG-ACRIN[*] Cancer Research Group and SOAPP Study Steering Committee in accessing these data is acknowledged. The results and conclusions in this paper are those of the authors and do not indicate concurrence by ECOG-ACRIN or the SOAPP Study Steering Committee.

[*] A merger of the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN)

Participants

Outpatients at least 18 years of age at any stage of care for invasive breast, lung, prostate, or colorectal cancer were eligible to participate; respondents with inadequate cognitive function (assessed by a study screener) were excluded.[171] Our analyses included participants whose hypnotic use was the same at both visits (i.e., 'yes' at both visits for the same hypnotic, or 'no' at both visits).

Study variables

At intake and approximately four weeks later, participants were asked to score their symptom severity at its worst in the past 24 hours on a scale from 0='not present' to 10='as bad as you can imagine'. Nineteen symptoms were evaluated: hair loss, appetite loss, memory loss, constipation, cough, feeling depressed, diarrhea, feeling distressed (upset), drowsiness, dyspnea, fatigue, nausea, nerve pain, pain, itching, disturbed sleep, sore mouth, vomiting, and dry mouth.[224] The survey was an expansion of the 13-item MD Anderson Symptom Inventory (MDASI), which also included six health-related quality of life (HRQoL) measures: general activity, mood, work relations with other people, walking, and enjoyment of life. Participants were asked to indicate the extent to which symptoms interfered with each HRQoL item on a scale from 0='Did not interfere' to 10='interfered completely'. A systematic review of HRQoL studies found that the detection threshold for meaningful change was, in many cases, one-half standard deviation.[176] In MDASI validation studies, standard deviations for symptoms ranged from 1.95 to 2.31; the authors therefore suggest a 1-point change may be minimally important (i.e., clinically significant).[175] Recognizing that an ideal method for determining clinical significance has yet to be established, and that results may vary across subpopulations even when methods are consistent,[177,225] the present study nonetheless assumes a 1-point change in symptom severity to be clinically meaningful.

Demographic information was collected from participants at intake, and clinicians provided clinical data and medication lists at intake and follow-up.

Statistical methods

Software

Statistical analyses were conducted using the following software: Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) and the Stata module PSMATCH2 (version 4.0.11, 2014).[184], SAS (SAS Institute. 2015. The SAS system for Windows. Release 9.4. SAS Institute, Cary, NC.), and IVEware (University of Michigan. 2002. IVEware: Imputation and Variance Estimation Software).

Missing data imputation

The percentage of missing values was low (<4%) for most independent variables, except ethnicity (7.18%). With a large number of variables, however, listwise deletion would reduce the sample by about 25%. Using SAS software and a callable routine built with IVEWare, values were multiply imputed (m=5) through sequential multiple regression by chained equations to accommodate heterogeneity of variable type and distribution.[201-203] Comparison of imputed datasets by analysis of variance (ANOVA) revealed no differences for any variables of interest. Analyses were, therefore, performed on a singly-imputed dataset, to facilitate use of advanced analytic procedures.

Matching cases and comparators

Participants not using hypnotics were matched to hypnotic users on the basis of Mahalanobis distance within calipers of 0.2 standard deviations of a propensity score.[209] Propensity scores, representing the probability of being in the treatment group were estimated with a probit model of baseline characteristics thought to predict treatment.[210] The variables used for matching were: age, sex, race, ethnicity, primary cancer site, history of depression, and sleep disturbance severity score at intake. The Mahalanobis metric is a multidimensional measure of distance between two observations.[211] Each estimate can be used alone to select matches, but use of both, first identifying candidates whose propensity scores are within calipers, then selecting from those based on minimal Mahalanobis distance, appears to provide more balanced samples than either method alone.[209] Average outcomes in the hypnotics group were estimated based on the average of differences across matched cases, and conditional variance was estimated using fifty neighbors (~12.5% of the group size) to produce heteroscedasticity-consistent standard errors.[212] Comparator cases were weighted based on the frequency with which they were used as controls. Matching was conducted to reduce the effects of selection bias (where covariates can have confounding effects on outcomes),[210] and to reduce Type-I error risk from heteroscedasticity (exacerbated by unequal group sizes).[213]

Statistical tests

The main hypotheses of interest were 1.) to compare changes in symptom severity and HRQoL between hypnotic users and non-users, and 2.) to assess the relationship between changes in sleep disturbance and changes in other symptoms and HRQoL. Hotelling's T^2 test (an omnibus version of the paired t-test[214]), with degrees of freedom corrected for heteroscedasticity,[215] was used to compare changes in symptom severity and

HRQoL between hypnotic users and non-users. Following a statistically significant multivariate result, post-hoc two-sided t-tests (with Welch's approximation of degrees of freedom for unequal variance) were performed to evaluate individual symptoms. Multivariate regressions were conducted to evaluate how sleep disturbance severity change related to changes in other cancer symptoms and HRQoL, controlling for hypnotic use. Significance level was set to $p < 0.01$ for all analyses.

Results

Sample characteristics

A total of 2,217 participants met the inclusion criteria; of these, 456 used hypnotics and 1,761 were non-users. The matching procedure identified 411 cases of hypnotic use that were matched to 1,241 weighted comparators, for a total weighted sample size of 822. The distribution of propensity scores across the two groups was similar, and two additional metrics for covariate balance are presented in **Table 3.12**: a.) standardized difference in percent of bias, and b.) two-sided t-tests for equality of means in the two samples.

Table 3.12 Covariate balance, before and after matching, between the treatment (Hypnotic Use) and weighted comparator (No Hypnotic Use) groups

Variable	Unmatched(U) Matched (M)	Mean Treated	Mean Control	% Bias[a]	% Reduction |bias|	t-test[b] t	t-test[b] p>|t|
Age Group							
	U	1.90	2.21	-26.4		-4.99	0.000
	M	1.93	1.93	0.0	100.0	0.00	1.000
Ethnicity							
	U	0.96	0.92	16.5		2.89	0.004
	M	0.98	0.98	0.0	100.0	0.00	1.000
Race							
	U	0.10	0.18	-20.0		-3.58	0.000
	M	0.07	0.07	0.0	100.0	0.00	1.000
Sex							
	U	0.77	0.69	18.8		3.48	0.001
	M	0.79	0.79	0.0	100.0	0.00	1.000
History of depression							
	U	0.43	0.23	42.6		8.52	0.000
	M	0.40	0.40	0.0	100.0	0.00	1.000
Primary cancer site							
	U	0.91	0.89	1.4		0.27	0.790
	M	0.82	0.82	0.0	100.0	0.00	1.000
Sleep disturbance severity at intake							
	U	1.35	0.90	43.6		8.53	0.000
	M	1.30	1.30	0.0	100.0	0.00	1.000

a. Standardized difference in percent bias is the percent difference in group means divided by the square root of the average variance.
b. Two sided t-test for equality of means in treatment versus comparator group.

Initial symptom severity scores are shown in **Table 3.13**. Disturbed sleep was the second most severely scored symptom with a mean (± standard deviation) score of 3.39 (±3.08). It should be noted that this measure was used for statistical matching, thus both groups share the same mean. Severity of four symptoms (hair loss, pain, diarrhea, and mouth sores) differed between groups, with the more severe scores always occurring in the hypnotic-user group.

Table 3.13 Initial symptom severity scores for the total sample, treatment group (Hypnotic Use), and weighted comparator group (No Hypnotic Use), ordered by decreasing severity for total sample.

	Total Sample		**No Hypnotic Use**		**Hypnotic Use**			
Symptom	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**t-test**	***p***
Fatigue	4.07	(2.88)	3.84	(2.82)	4.29	(2.93)	2.23	0.026
Disturbed sleep	3.39	(3.08)	3.39	(3.02)	3.39	(3.15)	-0.01	0.992
Drowsiness	3.09	(2.79)	3.05	(2.74)	3.12	(2.84)	0.40	0.689
Hair loss	2.53	(3.59)	2.13	(3.38)	2.93	(3.79)	3.21	0.001*
Feeling distressed	2.50	(2.71)	2.33	(2.52)	2.67	(2.89)	1.79	0.074
Memory loss	2.49	(2.58)	2.47	(2.54)	2.50	(2.62)	0.12	0.903
Dry mouth	2.48	(3.04)	2.36	(3.15)	2.60	(2.92)	1.14	0.256
Feeling depressed	2.27	(2.66)	2.04	(2.42)	2.51	(2.89)	2.50	0.013
Numbness/tingling	2.27	(2.83)	2.17	(2.68)	2.37	(2.98)	1.02	0.307
Pain	2.09	(2.67)	1.81	(2.46)	2.38	(2.87)	3.10	0.002*
Shortness of breath	1.86	(2.55)	1.77	(2.51)	1.96	(2.60)	1.07	0.287
Constipation	1.77	(2.73)	1.58	(2.56)	1.97	(2.89)	2.02	0.044
Appetite loss	1.75	(2.63)	1.58	(2.44)	1.91	(2.80)	1.85	0.065
Cough	1.42	(2.30)	1.45	(2.29)	1.39	(2.31)	-0.38	0.704
Diarrhea	1.30	(2.43)	0.94	(2.19)	1.67	(2.66)	4.29	<0.001*
Nausea	1.06	(2.14)	0.94	(1.95)	1.18	(2.32)	1.60	0.111
Itching	0.89	(2.15)	0.85	(2.18)	0.94	(2.13)	0.57	0.571
Mouth sores	0.75	(1.80)	0.55	(1.48)	0.94	(2.07)	3.10	0.002*
Vomiting	0.39	(1.46)	0.34	(1.27)	0.45	(1.62)	1.15	0.251

SD: standard deviation

Initial scores for symptom burden interference with HRQoL are shown in **Table 3.14**. Severity of three HRQoL measures (work, activity, and mood) differed between groups, with the more severe scores always occurring in the hypnotic-user group.

Table 3.14 Initial scores for symptom burden interference with health-related quality of life (HRQoL) for the total sample, treatment group (Hypnotic Use), and weighted comparator group (No Hypnotic Use), ordered by decreasing severity for total sample.

	Total Sample		No Hypnotic Use		Hypnotic Use			
HRQoL Measure	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**t-test**	***p***
Work	3.08	(3.04)	2.73	(2.81)	3.42	(3.25)	3.26	0.001*
Activity	2.92	(2.88)	2.60	(2.66)	3.24	(3.09)	3.18	0.002*
Walking	2.71	(3.05)	2.46	(2.82)	2.95	(3.26)	2.30	0.021
Enjoyment of life	2.61	(2.94)	2.39	(2.82)	2.82	(3.06)	2.09	0.036
Mood	2.45	(2.71)	2.16	(2.57)	2.73	(2.84)	3.02	0.003*
Relationships	1.70	(2.54)	1.62	(2.52)	1.78	(2.56)	0.90	0.367

SD: standard deviation

MANOVA: Hypnotic use and changes in symptom severity and HRQoL

The test for differences across mean changes in symptom severity between hypnotic users and non-users was significant ($F(19,720.8) = 16.51$, $p<0.001$). Results of *post hoc* individual t-tests are shown in **Table 3.15**. Changes in severity were different for all symptoms except: cough, hair loss, mouth sores, and vomiting. Hypnotic users reported decreased severity for all remaining symptoms except one: diarrhea. The symptom with the largest between-group mean [standard error] difference was numbness/tingling (1.29 [0.13]), followed by sleep (1.02 [0.16]). No differences in HRQoL measures were found on the basis of hypnotic use ($F(6,590.5) = 0.68$, $p=0.6682$).

Table 3.15 Individual Welch's two-sided t-tests to detect differences in symptom severity change on the basis of hypnotic (benzodiazepine/benzodiazepine receptor agonist) use.

Symptom	***Overall N=1652*** Mean	(SD)	***No Hypnotic Use N=411*** Mean	(SD)	***Hypnotic Use N=411*** Mean	(SD)	***Mean Difference***	***(SE)***	***t***	***df***	***p***
Numbness/tingling	0.91	(2.82)	1.24	(2.96)	-0.06	(2.08)	**1.29**	(0.13)	9.76	999	<0.001*
Disturbed sleep	0.07	(2.51)	0.32	(2.30)	-0.70	(2.95)	**1.02**	(0.16)	6.42	585	<0.001*
Feeling distressed	0.25	(2.30)	0.48	(2.23)	-0.45	(2.37)	**0.92**	(0.13)	6.96	668	<0.001*
Fatigue	0.06	(2.34)	0.27	(2.29)	-0.57	(2.40)	**0.84**	(0.13)	6.21	676	<0.001*
Appetite loss	0.57	(2.20)	0.75	(2.22)	0.04	(2.05)	**0.70**	(0.12)	5.92	755	<0.001*
Nausea	0.20	(1.97)	0.37	(1.94)	-0.30	(1.97)	**0.67**	(0.11)	5.97	693	<0.001*
Constipation	0.35	(2.52)	0.51	(2.63)	-0.13	(2.10)	**0.64**	(0.13)	5.05	872	<0.001*
Itching	0.20	(1.82)	0.35	(1.68)	-0.26	(2.13)	**0.61**	(0.12)	5.33	590	<0.001*
Drowsiness	0.02	(2.33)	0.16	(2.31)	-0.38	(2.35)	**0.54**	(0.13)	4.02	692	<0.001*
Shortness of breath	0.21	(1.71)	0.32	(1.67)	-0.15	(1.76)	**0.48**	(0.10)	4.81	674	<0.001*
Feeling depressed	0.11	(2.09)	0.22	(2.07)	-0.21	(2.10)	**0.43**	(0.12)	3.58	693	<0.001*
Memory loss	0.01	(2.19)	0.11	(2.19)	-0.30	(2.16)	**0.41**	(0.12)	3.35	711	<0.001*
Dry mouth	0.21	(2.15)	0.30	(2.06)	-0.06	(2.37)	**0.35**	(0.13)	2.70	629	0.007*
Pain	0.24	(2.04)	0.31	(2.05)	0.00	(2.00)	**0.30**	(0.11)	2.69	720	0.007*
Diarrhea	-0.24	(2.09)	-0.37	(2.19)	0.14	(1.68)	**-0.51**	(0.10)	-4.93	911	<0.001*
Hair loss	-0.29	(3.27)	-0.35	(3.39)	-0.11	(2.86)	**-0.24**	(0.17)	-1.41	823	0.158
Mouth sores	0.09	(1.57)	0.07	(1.51)	0.17	(1.74)	**-0.10**	(0.10)	-1.03	627	0.305
Cough	-0.24	(1.60)	-0.25	(1.60)	-0.21	(1.60)	**-0.03**	(0.09)	-0.37	699	0.709
Vomiting	0.02	(1.24)	0.03	(1.24)	0.00	(1.23)	**0.02**	(0.07)	0.33	711	0.739

SD: standard deviation; SE: standard error

Multivariate regression: symptom burden onto hypnotic use and sleep disturbance severity change

Table 3.16 provides results for the multivariate regression of changes in cancer symptom severity onto both hypnotic use and change in sleep disturbance severity (SDS). Symptoms are listed in decreasing order of R^2 for the overall model (i.e., both hypnotic use and SDS as independent variables).

Sleep disturbance. For all symptoms, increased SDS was associated with increased severity. The strongest associations were with: feeling distressed, dry mouth, and fatigue. For those symptoms, hypnotic use and SDS change together accounted for 25%, 20%, and 17%, respectively, of variance in symptom severity change. For these symptoms, the increases in severity corresponding with a 1-point increase in SDS were: (reported with regression coefficient [b] ± standard error):

- 0.46-point increase in feeling distressed (b: 0.46 ±0.02, $p<0.001$)
- 0.38-point increase in dry mouth (b: 0.38 ±0.02, $p<0.001$), and
- 0.37-point increase in fatigue (b: 0.37 ±0.02, $p<0.001$).

The weakest associations (model $R^2 = 0.05$) were observed with numbness/tingling (b: 0.26 ±0.03, $p<0.001$) and pain (b: 0.18 ±0.02, $p<0.001$). Regardless of statistical significance, low R^2 values (<0.05) for the following symptoms suggest little meaningful relationship with SDS: itching, hair loss, constipation, diarrhea, and mouth sores.

Hypnotic use. Hypnotic use was associated with changes in only one symptom. Holding changes in SDS constant, use of hypnotics was associated with a 0.31 decrease in fatigue (b: -0.31 ±0.11, $p=0.004$). Together, hypnotic use and SDS change accounted for 17% of the change in fatigue severity.

Table 3.16 Multivariate regression evaluating changes in cancer symptom severity associated with change in sleep disturbance severity, controlling for benzodiazepine/benzodiazepine receptor agonist hypnotic use.

Symptom		**Coefficient**	**(SE)**	**Model R^2**	**t**	**p**
Feeling distressed	SDS increase	0.46	(0.02)	0.25	23.15	<0.001*
	Hypnotic use	-0.13	(0.10)		-1.26	0.207
Dry mouth	SDS increase	0.38	(0.02)	0.20	19.99	<0.001*
	Hypnotic use	0.21	(0.10)		2.19	0.029
Fatigue	SDS increase	0.37	(0.02)	0.17	17.28	<0.001*
	Hypnotic use	-0.31	(0.11)		-2.92	0.004*
Shortness of breath	SDS increase	0.26	(0.02)	0.14	16.28	<0.001*
	Hypnotic use	0.03	(0.08)		0.36	0.722
Feeling depressed	SDS increase	0.30	(0.02)	0.13	15.84	<0.001*
	Hypnotic use	0.00	(0.10)		0.03	0.974
Drowsiness	SDS increase	0.30	(0.02)	0.11	13.84	<0.001*
	Hypnotic use	-0.17	(0.11)		-1.55	0.122
Nausea	SDS increase	0.24	(0.02)	0.10	12.99	<0.001*
	Hypnotic use	-0.13	(0.09)		-1.37	0.170
Cough	SDS increase	0.19	(0.02)	0.09	12.33	<0.001*
	Hypnotic use	-0.08	(0.08)		-1.05	0.296
Memory loss	SDS increase	0.22	(0.02)	0.07	10.75	<0.001*
	Hypnotic use	-0.15	(0.11)		-1.40	0.163
Vomiting	SDS increase	0.13	(0.01)	0.07	11.34	<0.001*
	Hypnotic use	0.10	(0.06)		1.61	0.107
Appetite loss	SDS increase	0.23	(0.02)	0.06	10.61	<0.001*
	Hypnotic use	0.20	(0.11)		1.85	0.065
Numbness/tingling	SDS increase	0.26	(0.03)	0.05	8.92	<0.001*
	Hypnotic use	0.12	(0.14)		0.83	0.406
Pain	SDS increase	0.18	(0.02)	0.05	9.34	<0.001*
	Hypnotic use	0.13	(0.10)		1.34	0.180
Itching	SDS increase	0.10	(0.02)	0.02	5.65	<0.001*
	Hypnotic use	-0.19	(0.09)		-2.13	0.033
Constipation	SDS increase	0.13	(0.02)	0.02	5.36	<0.001*
	Hypnotic use	-0.04	(0.13)		-0.30	0.762
Diarrhea	SDS increase	0.06	(0.02)	0.01	3.05	0.002*
	Hypnotic use	0.19	(0.10)		1.80	0.072
Mouth sores	SDS increase	0.03	(0.02)	0.01	1.97	0.049
	Hypnotic use	0.19	(0.08)		2.42	0.016
Hair loss	SDS increase	-0.02	(0.03)	0.00	-0.67	0.503
	Hypnotic use	-0.12	(0.16)		-0.76	0.445

SDS: sleep disturbance severity; SE: standard error

Multivariate regression: HRQoL onto hypnotic use and sleep disturbance severity change

Table 3.17 provides results for the multivariate regression of HRQoL measures onto both hypnotic use and change in sleep disturbance severity (SDS). HRQoL items are listed in decreasing order of R^2 for the overall model (i.e., hypnotic use and change in SDS as independent variables).

Sleep disturbance. Increased SDS was associated with increased interference for all HRQoL measures, except work. None of the associations, however, were strong. The largest proportion of variance explained by SDS change and hypnotic use was 6%, for mood ($R^2 = 0.06$); a 1-point increase in SDS was associated with a 0.23-point increase in overall symptom burden interference with mood (b: 0.23 ±0.02, $p<0.001$).

Hypnotic use. Holding changes in SDS constant, hypnotic use was associated with a 0.4-point increase in symptom burden interference with work:(b: 0.41 ±0.14, $p=0.003$).

A second multivariate analysis was performed to control for changes in all other symptoms. The model R^2 values shown in **Table 3.18** reflects the entire set of independent variables (i.e., hypnotic use, change in SDS, and all other symptom changes as independent variables). Notably, inclusion of all symptoms in models increased the proportion of variance in HRQoL explained by about ten-fold for all items, except work.

Sleep disturbance. After controlling for changes in other symptoms, only two HRQoL items (mood, enjoyment) were associated with SDS. Regression coefficients were vanishingly small, however, and negative, suggesting slightly improved HRQoL with increased SDS. The largest proportion of variance explained by SDS change and hypnotic use was 6%, for mood ($R^2 = 0.06$); a 1-point increase in SDS was associated with a 0.23-point increase in overall symptom burden interference with mood (b: 0.23 ±0.02, p<0.001).

Hypnotic use. Virtually identical with the previous model, holding changes in all symptoms constant, hypnotic use was associated with a 0.4-point increase in overall symptom burden interference with work:(b: 0.41 ±0.14, p=0.003).

Table 3.17 Multivariate regression evaluating changes in health-related quality of life associated with change in sleep disturbance severity, controlling for BZD/BzRA hypnotic use.

Symptom		**Coefficient**	**(SE)**	**Model R^2**	***t***	***p***
Mood	SDS increase	0.23	(0.02)	0.06	10.2	<0.001*
	Hypnotic use	-0.02	(0.11)		-0.2	0.845
Activity	SDS increase	0.24	(0.03)	0.04	7.98	<0.001*
	Hypnotic use	-0.08	(0.15)		-0.52	0.602
Enjoyment	SDS increase	0.20	(0.02)	0.04	7.98	<0.001*
	Hypnotic use	-0.20	(0.12)		-1.61	0.109
Relationships	SDS increase	0.18	(0.02)	0.04	7.93	<0.001*
	Hypnotic use	-0.04	(0.11)		-0.37	0.711
Walking	SDS increase	0.20	(0.03)	0.03	7.47	<0.001*
	Hypnotic use	0.11	(0.13)		0.82	0.414
Work	SDS increase	0.06	(0.03)	0.01	2.29	0.022
	Hypnotic use	0.41	(0.14)		2.99	0.003*

BZD: benzodiazepine; BzRA: BZD receptor agonist; SDS: sleep disturbance severity; SE: standard error

Table 3.18 Multivariate regression evaluating changes in health-related quality of life associated with change in sleep disturbance severity, controlling for BZD/BzRA hypnotic use and for changes in all other symptoms.

Symptom		**Coefficient**	**(SE)**	**Model R^2**	***t***	***p***
Mood	SDS increase	-0.07	0.03	0.46	-3.19	0.001*
	Hypnotic use	0.06	0.09		0.71	0.480
Activity	SDS increase	-0.07	0.03	0.54	-2.54	0.011
	Hypnotic use	-0.03	0.11		-0.26	0.798
Enjoyment	SDS increase	-0.09	0.02	0.47	-3.65	<0.001*
	Hypnotic use	-0.19	0.10		-1.95	0.052
Relationships	SDS increase	0.04	0.03	0.35	1.60	0.110
	Hypnotic use	-0.12	0.10		-1.27	0.205
Walking	SDS increase	-0.02	0.03	0.36	-0.68	0.495
	Hypnotic use	0.18	0.11		1.63	0.103
Work	SDS increase	0.03	0.04	0.01	0.81	0.420
	Hypnotic use	0.41	0.14		2.95	0.003*

BZD: benzodiazepine; BzRA: BZD receptor agonist; SDS: sleep disturbance severity; SE: standard error

Discussion

Sleep disturbance is a well-recognized problem for persons with cancer, and hypnotic use is common in this population. Relationships between disturbed sleep and cancer-related pain, fatigue, and depression are well documented, but interactions with other cancer symptoms have not been well studied. Little is known, also, about the effects of hypnotics in persons with cancer, whose response may be mediated by the complexities of disease status and medication regimens. We conducted this study to contribute to those knowledge gaps.

Symptom burden

Hypnotic use. Comparing BZD/BzRA hypnotic users against non-users, we found that hypnotic users reported decreased severity for most, but not all, symptoms. Assuming a 1-point change to be the minimum threshold for clinical significance, three symptoms stood out: numbness/tingling, disturbed sleep, and feeling distressed (1.3-point, 1.0-point, and 0.9-point reductions, respectively). With hypnotic use, decreased sleep disturbance severity (SDS) was an expected finding. Decreased distress is also unsurprising; BZDs, which are anxiolytic as well as sedating, comprised 74% of the hypnotics used. We did find it noteworthy, however, that the largest change was seen in numbness/tingling. BZDs are not recommended for treatment of neuropathic pain, but their mechanism of action is similar to other agents used for this indication.[305,306] Gabapentin and pregabalin are considered first-line agents for chemotherapy-induced neuropathy.[307] These anticonvulsants act to increase levels of γ-aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter in the central nervous system.[133] BZDs bind near type A receptor sites for GABA, and act to enhance its inhibitory effects.[308] Because GABA-A receptors are widespread throughout the nervous system, drugs – such as BZDs – that are non-selective for receptor subtypes can have a broad range of activity, including sedative, hypnotic, anxiolytic, myorelaxant, amnestic, and anasthetic effects. BZD receptor agonists (BzRAs) such as zolpidem and zaleplon, on the other hand, have primarily hypnotic effects because they are selective for $\alpha 1$ subtypes (which primarliy mediate sleep).[125] Thus, while there is some evidence that BZDs can attenuate neuropathic pain,[309] concerns over side effects limit their appeal. In persons with cancer, in particular, BZD use has been associated with daytime drowsiness, dry mouth, morning delerium, and respiratory depression.[146,147] Nonetheless, our findings lend support for the hypothesis that drugs specifically targeting the subtype(s) of GABA-A receptors involved in transmission of pain signals (most likely, $\alpha 2$, $\alpha 3$, and $\alpha 5$) may be effective for controlling neuropathic pain.[310] Retrospective evaluations of GABA-ergic drug use in persons with cancer may provide insights to supplement the current body of preclinical findings.

Change in sleep disturbance severity. Sleep disturbance has often been observed to occur concurrently with cancer-related fatigue, depression, and pain,[118,120,304] and this was borne out in our study, as well. Our results stand out from prior studies, however, in finding significant relationships with thirteen additional symptoms: feeling distressed, dry mouth, shortness of breath, drowsiness, nausea, cough, memory loss, vomiting, appetite loss, numbness/tingling, pain, itching, constipation, and diarrhea. We also note the relatively small association between sleep and pain, despite the frequency with which those two symptoms are identified together in symptom clusters. Attempts to identify symptom clusters are motivated, in part, by the possibility of discovering a single underlying cause to target therapeutically.[235] Characterization of clusters may be subject to information bias, however, because pain and fatigue are among the most commonly measured symptoms.[169] In this study, the symptoms most strongly associated with sleep disturbance were: feeling distressed, fatigue, dry mouth, and shortness of breath. While we cannot determine underlying causal pathways and directions from this study, our findings suggest that sleep is integrally related not just to a few symptoms, but to overall symptom burden. Prospective studies measuring sleep and symptom burden both subjectively and objectively would be needed to confirm this.

We were unable to evaluate the extent to which initiation of hypnotic use changed severity of sleep disturbance in this study because patients were evaluated during the course of treatment, rather than at initiation. We did control for hypnotic use, however, when evaluating associations between SDS change and changes in other symptoms. Only one symptom, fatigue, changed with hypnotic use (0.31-point decrease in severity), suggesting that much of the difference in symptom burden between BZD/BzRA hypnotic users and non-users may be mediated by changes in sleep disturbance.

Health-related quality of life

Hypnotic use. For items measuring symptom burden interference with health-related quality of life (HRQoL), MANOVA revealed no differences in severity change between hypnotic users and non-users. Although some improvements to HRQoL have been observed in clinical trials of BzRA hypnotics,[311,312] our null findings are consistent with prior studies in general populations. In a survey of almost 3,000 subjects in Japan (where BZDs comprised about 40% of hypnotics used),[144] insomniacs using hypnotics had lower mental and physical HRQoL scores than non-using insomniacs.[64] The investigators suggested that gains in sleep may have been overshadowed by next-day residual adverse effects of BZDs (e.g., sedation, amnesia, myorelaxation).[64] More recently, in a nationally-representative United States sample (N=104,274), participants with insomnia reported the same reductions in physical and mental HRQoL regardless of whether or not they used BZD/BzRA hypnotics (17% of hypnotics used were BZDs).[313] Comparisons across studies may not be valid, however, as each used different measures for HRQoL. Furthermore, the HRQoL portion of the MDASI survey has not been evaluated for sensitivity to detect changes related to sleep disturbance or its treatment.

Change in sleep disturbance severity. Controlling for hypnotic use, increased SDS was associated with increased symptom burden interference for all HRQoL measures, except work. A note of caution is due here, since only 18% of participants worked full-time (27% worked part-time, 56% were unemployed). Although the item was worded as "work (including work around the house)", it is possible that participants experiencing difficulties with symptom burden scored interference with work low simply because they were not working. We also note that relationships with other HRQoL measures were not strong. Models explained $\leq 6\%$ of variance in HRQoL and regression coefficients were ≤ 0.24. When we performed a second analysis including all symptom changes as covariates, the models accounted for substantially more variance. Relationships between SDS and HRQoL virtually disappeared, however, suggesting that relationships between sleep disturbance and HRQoL, as detected by this instrument, were mediated by other symptoms.

Interestingly, we noted a 0.4-point increase in interference with work associated with hypnotic use. This result is difficult to interpret, however, as the model accounted for only 1% of variance, and results of the MANOVA indicated no such relationship. Furthermore, while it is a known problem that both BZD and BzRAs can produce next-day sedation that may affect daytime performance,[9,314] in this sample they were associated with a slight (0.31-point) improvement to fatigue. These contradictions may reflect differing needs and symptom burdens between patients who are working and those who have reduced their workload or stopped working altogether.

Strengths & Limitations

This study benefitted from a longitudinal, rather than cross-sectional design, which allowed evaluation of change. A major limitation, however, was that it evaluated patients during the course of treatment, rather than at initiation. Thus, we were unable to evaluate the extent to which initiation of hypnotic use changed severity of sleep disturbance. Having a large initial sample permitted statistical matching of comparators to cases, which can reduce selection bias in a retrospective study and more closely approximate a randomized controlled design. We could not control for unmeasured confounders, however, and cannot be certain that all important covariates were included in the matching models. Residual confounding may remain. Results may also be confounded by undocumented use of other sleep aids, including over-the-counter medications, off-label drugs, and alcohol, or by non-adherence to prescribed hypnotics. Surveys are subject to recall bias, and the sensitivity of the MDASI survey instrument to assess changes in HRQoL related to sleep has not been evaluated. Finally, our results may not be generalizable beyond ambulatory solid-tumor cancer patients treated by an oncology group in the Eastern United States. These limitations notwithstanding, our findings have revealed relationships that should be further explored in prospective trials.

Conclusions

Sleep disturbance (SD) is recognized as one of the most common and most severe cancer symptoms,[82,90,110] and benzodiazepines (BZDs) and benzodiazepine receptor agonists (BzRAs) are frequently used in this setting,[140-142,258] even though there is little evidence to guide their use. To address this gap, we evaluated symptom burden and health-related quality of life outcomes associated with sleep disturbance and hypnotic use in a large sample of participants with solid tumors. Cancer-related pain, fatigue, and depression have commonly been associated with sleep disturbance, but we found that relationships may exist for many other symptoms. Sleep disturbance also appears to correlate with reduced health-related quality of life, but this may depend on interactions between disturbed sleep and other cancer symptoms. Given the multifarious somatic effects of sleep, however, it is reasonable to hypothesize that effective management of sleep disturbance is essential to minimizing burden from a wide spectrum of symptoms. Studies testing this hypothesis may help to better define relationships between symptoms and uncover causal pathways.

Use of BZD/BzRA hypnotics in this study correlated with lower overall symptom burden, but the extent to which this was mediated by effects on sleep – versus other effects of the drugs – was unclear. Two new drug classes have been developed for treatment of insomnia (melatonin receptor agonists, dual-acting orexin antagonists), and a few others (including antidepressants, anticonvulsants, and antipsychotics) are now recognized to have sleep-promoting effects. With different mechanisms of action, each drug class also has unique effects on sleep, as well as a particular set of other therapeutic actions. Future studies designed to distinguish between sleep-related changes in symptom burden and non-sleep-related therapeutic effects of the drugs would allow clinicians to make more strategic prescribing decisions for patients with differing symptom burdens.

3.4 SECTION IV: TARGET JOURNALS

Table 3.19 is a listing of journals whose aims and scope are consistent with the manuscripts presented in this chapter. Because the studies in these manuscripts were specific to this country, all but one journal is based in the United States. Most journals listed a cost of $3,000 to $5,000 for the option of open access publishing, but no other publication charges were listed. The Source Normalized Impact per Paper (SNIP), a metric that takes into account the subject field of a publication,[d] is listed for each journal, along with sample papers on topics related to this project.

[d] Moed HF. Measuring contextual citation impact of scientific journals. *Journal of Informetrics*. 2010;4(3):265-277. doi:10.1016/j.joi.2010.01.002.

Table 3.19 Listing of target journals for manuscripts presented in this dissertation

Journal	Publisher / Organization	Aims & Scope
Supportive Care in Cancer SNIP: 1.291	Springer / Multinational Association of Supportive Care in Cancer	Scientific & social information on all aspects of supportive care in cancer. Primarily covers medical, technical and surgical supportive therapies. Nursing, rehabilitative, psychosocial and spiritual issues are also included.
Comparison of subgroups of breast cancer patients on pain and co-occurring symptoms following chemotherapy. Langford DJ, et.al. 2016 Identification of distinct subgroups of breast cancer patients based on self-reported changes in sleep disturbance. Van Onselen C, et.al. 2012		
Journal of Pain & Symptom Management SNIP: 1.483	Elsevier / American Academy of Hospice & Palliative Medicine, National Hospice & Palliative Care Organization	Interdisciplinary. Clinical research & best practices for relief of illness burden. Clinical trials, epidemiology, instrument development, health services studies, systematic and narrative reviews, case series and case reports
Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. Van Onselen C, et.al. 2013 Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. Kwekkeboom KL, et.al. 2010 Sleep-wake disturbances in patients with advanced cancer and their family carers. Gibbins J, et. al. 2009		
American Journal of Hospice and Palliative Care SNIP: 0.798	Prime National Publishing	Articles on multidisciplinary care, end of life issues, pain & symptom management psychosocial aspects, quality of care. Emphasis on information directly applicable to care of the patient/family at the bedside.
Insomnia in Patients With Advanced Cancer. Mellar P, et.al. 2013 An Observational Study of Insomnia and Nightmare Treated With Trazodone in Patients With Advanced Cancer. Hitoshi T, et.al. 2012		
Journal of Pain & Palliative Care Pharmacotherapy SNIP: 0.386	Taylor & Francis	Acute, chronic, and end-of-life symptom management.
Sedative-Hypnotics and the Treatment of Insomnia. Jill E. Allen & Christopher R. Jones. 2010 Quetiapine for Sleep. Scott Yost & Jacob White. 2010		
Journal of Psychosocial Oncology SNIP: 0.670	Taylor & Francis / Association of Oncology Social Work	Interdisciplinary: education, epidemiology, medical oncology, nursing, nutrition, physical therapy, psychiatry, psychology, public health, social work, surgical oncology. Exploratory, hypothesis testing, & program evaluation research.
Psychosocial resources and sleep disturbance before chemotherapy for gynecologic cancer. Bryan J, et.al. 2016 Exploring the Relationship Between Fear of Cancer Recurrence and Sleep Quality in Cancer Survivors. Berrett-Abebe J, et.al. 2015		

Chapter 4: Conclusions

The purpose of this project was to address substantial knowledge gaps in the literature pertaining to the management of sleep disturbance in persons with cancer. Even though sleep disturbance is recognized as one of the most common and most severe symptoms of cancer,[82,90,110] there is scant evidence to guide its treatment.[156,164] Data on oncology-specific contributing and mediating factors are needed for the development of preventative measures and recognition of at-risk patients. Research that documents the response of this unique population to hypnotic medications is vital to ensuring patients receive the safest and most effective treatments. As this knowledge base builds, evidence-based guidelines for management of cancer-related sleep disturbance can take shape. To that end, this project contributes the following findings:

1) Prevalence and correlates of sleep disturbance severity in a large sample of solid tumor cancer patients, and compared across cancer-specific subgroups;
2) Prevalence and correlates of benzodiazepine (BZD) and benzodiazepine receptor agonist (BzRA) hypnotic use in a large sample of solid tumor cancer patients, and compared across cancer-specific subgroups;
3) Changes in severity of cancer symptoms and in health-related quality of life associated with BZD/BzRA hypnotic use and with change in severity of sleep disturbance.

4.1 SECTION I: SUMMARY OF FINDINGS

4.1.1 Prevalence and correlates of sleep disturbance severity

The prevalence and correlates of sleep disturbance in oncology have been evaluated in several studies, but findings are difficult to synthesize due to heterogeneity in study populations, designs, and methods. An advantage for this study was the use of data from the Symptom Outcomes and Practice Patterns (SOAPP) survey, which provided not only a large and diverse sample of participants, but also substantially more variables than previous studies of cancer-related sleep disturbance. This, along with consistency in measurement of all symptom severity variables, allowed for meaningful comparisons of the relative importance of correlates within, and between, cancer-specific subsamples.

In this study, the most important correlates of sleep disturbance were other cancer symptoms. Notably, however, most symptoms were mild, on average, and severity seemed uncorrelated with sleep disturbance. Comparing across cancer-specific subgroups, distress was the only universal correlate, but cognitive difficulty, drowsiness, and fatigue were also common. Benzodiazepine receptor agonists, specifically indicated for insomnia, correlated with a small increase in sleep disturbance severity overall (no associations were found with benzodiazepines), while use of anticonvulsants for pain correlated with a relatively large decrease in severity of sleep disturbance for prostate cancer. These findings suggest that even when individual symptoms are mild, patients with multiple symptoms may experience substantially worsened sleep. For the symptom of distress, in particular, the consistency of its correlation with sleep disturbance may mark an important therapeutic target. In addition, identifying alternate therapies may be essential, as it appears from this study that standard pharmacotherapy for insomnia may not benefit persons with cancer as much as treatments that target multiple symptoms.

4.1.2 Prevalence and correlates of benzodiazepine (BZD) and benzodiazepine receptor agonist (BzRA) hypnotic use

Despite the prevalence of cancer-related sleep disturbance,[90] and a history of reliance on hypnotic medications,[137-139] little is known about current patterns of hypnotic use among oncology patients in the United States (US). Following the introduction of benzodiazepine receptor antagonists (BzRAs) in the late 20th century in the US, prescribing practices in the general population changed dramatically.[145] Benzodiazepines (BZDs) have fallen out of favor and the relatively safer BzRAs are now the drug of choice. It is unclear whether these changes extend to the oncology setting, but obtaining current data on which drugs are being prescribed, and how commonly, is an important first step in evaluating the management of sleep disturbance in persons with cancer.

Prevalence of hypnotic use, especially BZDs, in this sample was high relative to the general population, but low relative to the prevalence of sleep disturbance. Racial disparity was observed in this sample, with rates of hypnotic use two to three times higher among whites, as compared to blacks. Several sedating medications correlated with hypnotic use, including opioid analgesics and the strongly sedating anti-emetic promethazine. An association with clinician-identified distress was also noted, yet no association was found between clinician-identified sleep disturbance and hypnotic use. These findings raise concerns about under-treatment of sleep disturbance, which may be a function of patient help-seeking behavior, but may also reflect prescribers' attitudes toward medications, disagreement between patient reports and clinician assessments, and social determinants such as racial bias or access to care. Polypharmacy with sedatives and a heavy reliance on benzodiazepines are also concerning due to increased risk of drug interactions, including fatal respiratory depression with opioid analgesia.

4.1.3 Changes to cancer symptom burden and health-related quality of life associated with BZD/BzRA hypnotic use and with change in severity of sleep disturbance

Few studies have evaluated the outcomes associated with hypnotic use in people with cancer. As a result, current recommendations for management of cancer-related sleep-disturbance are guided primarily by studies in general populations.[156,157] It cannot be assumed, however, that standard therapies are appropriate; patients with cancer have additional sleep disturbance risk factors and markedly higher risks of adverse medication events and interactions. Conversely, some side-effects that are usually unwanted (e.g., weight gain) may be welcome in this setting. Observed clustering of certain symptoms (e.g., pain, fatigue, and sleep disturbance) may bespeak a common underlying biological pathway to target therapeutically, but identifying those relationships and characterizing the interactions are key to optimizing symptom management.

In this sample, reduced sleep disturbance severity (SDS), over approximately four weeks, correlated with improvement in nearly all symptoms measured, but most notably: distress, dry mouth, and fatigue. Reduced SDS also correlated with improved health-related quality of life (HRQoL), but this likely reflects interactions between sleep and other cancer symptoms. Use of hypnotics in this study appeared to have little correlation with HRQoL, but did correlate with lower overall symptom burden. The extent to which this was mediated by effects on sleep – versus other effects of the drugs – was unclear. These pan-symptom findings are consistent with the growing documentation of sleep-related activity in virtually all somatic systems, and indicate that future studies of cancer-related sleep disturbance, and treatments, should incorporate measures for a broad range of cancer symptoms. Distinguishing sleep-related changes in symptom burden from non-sleep-related effects of drugs would allow for more strategic management of patients with differing symptom burdens, and may shed light on underlying mechanisms.

4.2 SECTION II: RELEVANCE TO TRANSLATIONAL SCIENCE

This project can be classified as health outcomes research, which, on the spectrum of translational science, would be subsumed under clinical implementation and public health (sometimes referred to as T3 and T4, respectively). Inspiration for this study, however, spans the spectrum. The pervasiveness of cancer-related sleep disturbance, and its intractableness, were first observed during clinical practice. Merging knowledge of hypnotic pharmacology (molecular mechanisms of action for drugs) with sleep-related and cancer-related physiology (function and response of biological systems), resulted in the recognition that hypnotic use may yield different results in persons with cancer. The final impetus was the realization that no guidelines, and little evidence, existed for management of sleep disturbance specifically in persons with cancer.

4.2.1 Public health

Findings from this study on the prevalence and correlates of hypnotic use are applicable to health services research. First and foremost is the concern that sleep disturbance may be undertreated in persons with cancer, even when clinicians correctly identify sleep disturbance as a priority for their patients. To correct this, it will first be necessary to identify whether the barriers to treatment originate with prescribers (e.g., attitudes toward medication, perceptions of patients' needs), patients (e.g., help-seeking behavior), or elsewhere (e.g., coordination of care, health insurance restrictions). Notably, the racial disparity in hypnotic use found in this study may point to public health concerns such as access to care or provider bias.

The observation that BZDs, which have more side effects than BzRAs, are still in frequent use in the oncology setting should be further investigated. Unless there is evidence that the benefits of BZD use in this sensitive population outweigh the risks, interventions such as patient education and updated clinical guidelines may be warranted. Polypharmacy with sedative drugs should also be further evaluated. Retrospective analyses of large datasets may be useful for detecting the incidence of adverse events related to sedative polypharmacy in persons with cancer, and identifying those patients most at risk.

4.2.2 Clinical research

The primary opportunity for clinical research related to this study is the systematic evaluation of hypnotics (and other sleep-promoting drugs) in persons with cancer. Most importantly, the high rate of BZD and BzRA use found in this study warrants evaluation of their safety and efficacy of in cancer patients. In addition, the finding of less severe sleep disturbance in men with prostate cancer taking anticonvulsants could be followed up with a prospective study.

Among all possible correlates evaluated in this study, it was other cancer symptoms that most strongly correlated with sleep disturbance severity. Moreover, change in sleep disturbance severity was accompanied by change in nearly every symptom evaluated. Clinical research to evaluate these relationships (and their responses to therapies) can further our understanding of the complex interplay of cancer symptoms and their underlying causes. As this understanding improves, clinicians and researchers will be better able to strategically customize preventative and therapeutic approaches for their individual patients. Such findings would also help to focus drug development (or repurposing) efforts toward particular symptoms or symptom clusters.

The close relationship found in this study between distress and sleep disturbance represents a specific opportunity for clinical science. Both symptoms manifest in the physical as well as mental domains of health, and both can be treated non-pharmacologically as well as pharmacologically. As such, it is likely that multimodal and interprofessional approaches will produce the best results, but clinical trials will be necessary to determine the ideal configuration of therapeutic elements.

4.2.3 Pre-clinical and basic research

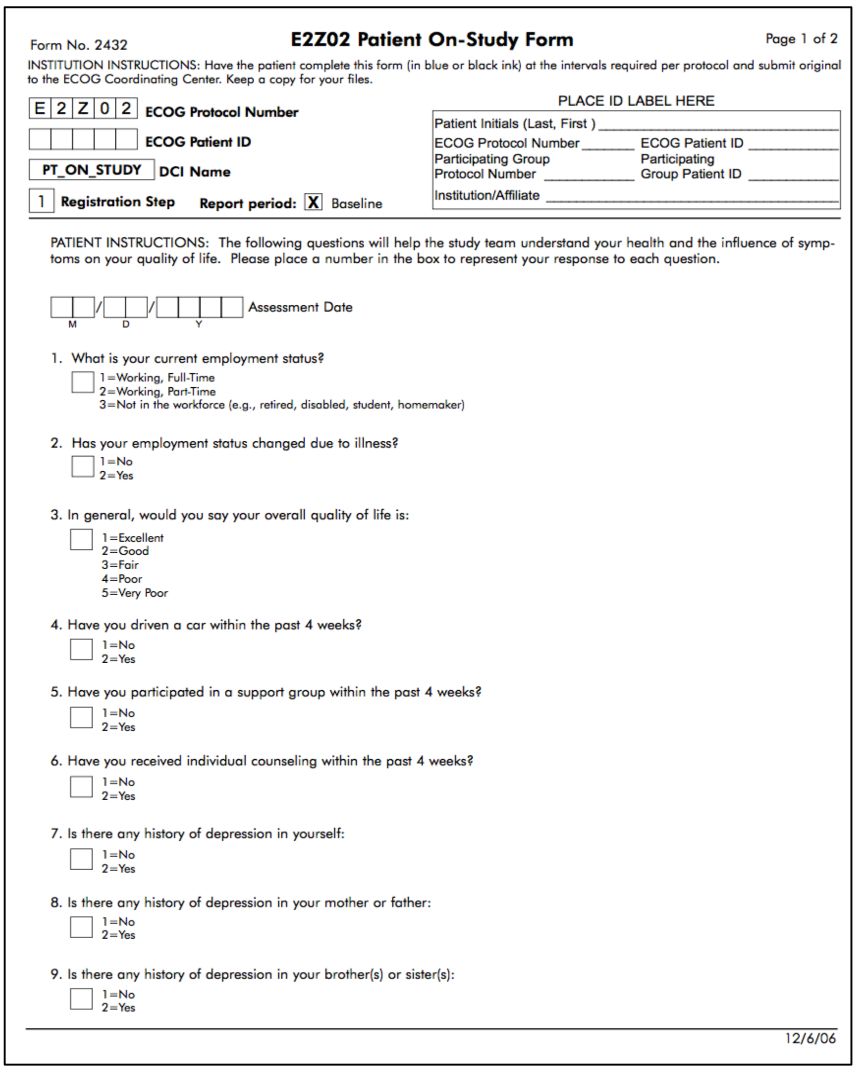
Relationships between sleep disturbance and other cancer symptoms can be studied pre-clinically by way of genome-wide association studies, which may help to uncover key biological processes and novel drug targets. Basic research and preclinical pharmacology studies can also aid in the interpretation of results from this study, and can help in determining the suitability of alternative therapies. For example, regulation of appetite and sleep tend to be in opposition, as evidenced by the neuropeptide orexin, which increases appetite and suppresses sleep. This study, however, found that appetite loss increased as sleep disturbance severity increased. If this finding is confirmed in other studies, it might suggest regulatory activity not yet characterized by basic scientists.

4.3 Section III: Future work

This project was undertaken as a preliminary contribution to the evaluation and improvement of current standards of care. If afforded the opportunity, future work would include additional "real-world" evaluations of hypnotic use with the goal of identifying and testing drugs already in use that can be repurposed or used more effectively for management of sleep disturbance and other symptoms of cancer.

Appendix A: Patient Survey

Patients participating in the Symptom Outcomes and Practice Patterns (SOAPP) study were asked to provide demographic information (Patient On-Study Form) and to complete a symptom severity and interference survey (MDASI-ECOG Form) at the initial visit. At the follow-up visit, approximately four weeks later, participants were asked to repeat the symptom severity and interference survey (MDASI-ECOG Form).


Form No. 2432 **E2Z02 Patient On-Study Form** Page 1 of 2

INSTITUTION INSTRUCTIONS: Have the patient complete this form (in blue or black ink) at the intervals required per protocol and submit original to the ECOG Coordinating Center. Keep a copy for your files.

E 2 Z 0 2 **ECOG Protocol Number**

ECOG Patient ID

PT_ON_STUDY **DCI Name**

1 **Registration Step** **Report period:** X Baseline

PLACE ID LABEL HERE

Patient Initials (Last, First) ______

ECOG Protocol Number ______ ECOG Patient ID ______

Participating Group Protocol Number ______ Participating Group Patient ID ______

Institution/Affiliate ______

PATIENT INSTRUCTIONS: The following questions will help the study team understand your health and the influence of symptoms on your quality of life. Please place a number in the box to represent your response to each question.

M / D / Y Assessment Date

1. What is your current employment status?
   1=Working, Full-Time
   2=Working, Part-Time
   3=Not in the workforce (e.g., retired, disabled, student, homemaker)

2. Has your employment status changed due to illness?
   1=No
   2=Yes

3. In general, would you say your overall quality of life is:
   1=Excellent
   2=Good
   3=Fair
   4=Poor
   5=Very Poor

4. Have you driven a car within the past 4 weeks?
   1=No
   2=Yes

5. Have you participated in a support group within the past 4 weeks?
   1=No
   2=Yes

6. Have you received individual counseling within the past 4 weeks?
   1=No
   2=Yes

7. Is there any history of depression in yourself:
   1=No
   2=Yes

8. Is there any history of depression in your mother or father:
   1=No
   2=Yes

9. Is there any history of depression in your brother(s) or sister(s):
   1=No
   2=Yes

12/6/06

(continued):

10. Overall, how much are you bothered by difficulties related to health problems other than cancer?
    ☐ 0=Not at all
    1=A little bit
    2=Moderately
    3=Quite a bit
    4=Extremely

11. Overall, how much are you bothered by <u>difficulties related directly to cancer?</u>
    ☐ 0=Not at all
    1=A little bit
    2=Moderately
    3=Quite a bit
    4=Extremely

12. Overall, how much are you bothered by <u>difficulties related to the treatment of cancer</u> (i.e. chemotherapy or other systemic therapy, radiation therapy, surgery)?
    ☐ 0=Not at all
    1=A little bit
    2=Moderately
    3=Quite a bit
    4=Extremely

13. Overall, how much are you bothered by <u>side effects from medications used to treat pain or other symptoms?</u>
    ☐ 0=Not at all
    1=A little bit
    2=Moderately
    3=Quite a bit
    4=Extremely

14. Did anyone come with you to this office visit?
    ☐ 1=No
    2=Yes

15. Overall, how much are you bothered by <u>weight gain or loss?</u>
    ☐ 0=Not at all
    1=A little bit
    2=Moderately
    3=Quite a bit
    4=Extremely

Form No. 2434

E2Z02 MDASI-ECOG Form

INSTITUTION INSTRUCTIONS: Have the patient complete this form (in blue or black ink) at the intervals required per protocol and submit original to the ECOG Coordinating Center. Keep a copy for your files.

E 2 Z 0 2 **ECOG Protocol Number**

ECOG Patient ID

MDASI **DCI Name**

1 **Registration Step**

PLACE ID LABEL HERE

Patient Initials (Last, First) ______

ECOG Protocol Number ______ ECOG Patient ID ______

Participating Group Protocol Number ______ Participating Group Patient ID ______

Institution/Affiliate ______

Report Period Choose one (☒) : ☐ **Baseline** ☐ **Follow-up** **Assessment Date** __ __ / __ __ / __ __ __ __ (M D Y)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering** things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

12/6/06

Form No. 2434
Patient Initials: Last ____ , First ____

E2Z02 MDASI ECOG Form

ECOG Patient ID ____________________

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **diarrhea (loose stools)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **mouth sores** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **skin rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **hair loss** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **coughing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
20. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
21. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
22. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
23. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
24. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
25. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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Appendix B: Clinician Survey

Clinicians participating in the Symptom Outcomes and Practice Patterns (SOAPP) study were asked to provide baseline clinical data (Baseline Data Form, Clinician On-Study Form) and to evaluate their patients' health-related quality of life (Clinician On-Study Form, Section 4) at the initial visit.

Form No. 2430

E2Z02 Baseline Data Form

Page 1 of 3

INSTRUCTIONS: Complete this form and submit original to the ECOG Coordinating Center within one week of registration. Keep a copy for your files.

E 2 Z 0 2 **ECOG Protocol Number**

ECOG Patient ID

BDF **DCI Name**

1 **Registration Step** **Report period:** X Baseline

PLACE ID LABEL HERE

Patient Initials (Last, First) ______

ECOG Protocol Number ______ ECOG Patient ID ______

Participating Group Protocol Number ______ Participating Group Patient ID ______

Institution/Affiliate ______

Please mark an 'X' if data have been amended
(Please circle amended items in red)

Date(s) Data Amended __/__/____ (M D Y)
__/__/____ (M D Y)

__/__/____ (M D Y) Assessment Date

Disease Characteristics

Primary Site(s) (Place an 'X' in the appropriate boxes)

- Breast
- Prostate
- Colorectal
- Lung

__/____ (M Y) Date of initial pathologic/clinical/radiographic diagnosis (Mark an 'X' if unknown)

If patient has multiple primaries, please indicate additional sites

01=Bone	10=Nodes
02=Brain	11=Skin
04=Effusion/Ascites	14=Pleura
05=GI (Other)	15=Leukemia
06=GU (Other)	16=Lymphoma
07=Head & Neck	99=Other, Specify______
08=Liver	

Disease Status

Current Status of Disease

1=CR (Complete Disappearance of Lesions)
2=PR (Partial Response)
3=SD (Stable)
4=PD (Progression)

Current Stage of Disease

1=NED (No evidence of disease)
2=Local/regional
3=Metastatic
4=Local/regional and metastatic

__/____ (M Y) Date of initial diagnosis of metastatic disease (if applicable) (Mark an 'X' if not applicable)

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Patient Initials: Last ____ , First ____ ECOG Patient ID ________________________

Disease Status (cont.)

Metastatic Site(s): (Please mark an 'X' for all that apply)

- [ ] Abdominal/visceral
- [ ] Brain
- [ ] Breast
- [ ] Bone
- [ ] Bone marrow
- [ ] Leptomeningeal or epidural
- [ ] Liver
- [ ] Lung
- [ ] Pleuritic
- [ ] Soft tissue/nodes
- [ ] Other________________
- [ ] Other visceral, specify____________

ECOG Performance Status (On date of this evaluation)

0=Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1=Restricted in physically strenuous activity but ambulatory (K 70-80)
2=Ambulatory and capable of all selfcare but unable to carry out any work activities (K 50-60)
3=Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours (K 30-40)
4=Completely disabled (K 10-20)

Weight loss in previous six months

1= <5% of body weight
2=5 - <10% of body weight
3=10 - <20% of body weight
4= ≥20% of body weight

Prior Treatment For Cancer

Has the patient had prior chemotherapy/immunotherapy/hormonal therapy?

1=No
2=Yes

If yes:

Total number of prior chemotherapy/immunotherapy/hormonal therapy regimens

1=1 Regimen
2=2 Regimens
3=3 or more Regimens

Prior radiation therapy?

01=No
02=Yes
-1=Unknown

Current Treatment For Cancer

Is the patient currently receiving treatment for cancer?

1=No (Follow-up only)(Skip remainder of form)
2=Yes

If yes:

Type of therapy patient is currently receiving

1=Adjuvant
2=Neoadjuvant
4=Recurrent/Non-metastatic
5=Metastatic

E2Z02 Baseline Data Form

Patient Initials: Last ____ , First ____ ECOG Patient ID ____________________

Current Treatment For Cancer (cont.)

Current chemotherapy/immunotherapy/hormonal therapy
01=No, 02=Yes, -1=unknown

- ☐☐ chemotherapy, single-agent cytotoxic systemic
- ☐☐ chemotherapy, multi-agent cytotoxic systemic
- ☐☐ chemotherapy, non-cytotoxic (e.g. endostatin, mmpi, TKI)
- ☐☐ chemotherapy – not otherwise specified (includes non-systemic chemotherapy)
- ☐☐ immunotherapy
- ☐☐ hormonal therapy

Current radiation therapy?
☐☐ 01=No
02=Yes
-1=Unknown

Start Dates of Current Treatment

	M	D	Y
Chemotherapy	☐☐ /	☐☐ /	☐☐☐☐
Immunotherapy	☐☐ /	☐☐ /	☐☐☐☐
Hormonal therapy	☐☐ /	☐☐ /	☐☐☐☐
Radiation therapy	☐☐ /	☐☐ /	☐☐☐☐

Investigator Signature ____________ Investigator Signature Date ____________

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Form No. 2431

E2Z02 Clinician On-Study Form

INSTRUCTIONS: Complete this form at the time of the initial visit and submit original to the ECOG Coordinating Center within one week of registration. Keep a copy for your files.

E 2 Z 0 2 **ECOG Protocol Number**

☐☐☐☐☐ **ECOG Patient ID**

CLIN_ON_STUDY **DCI Name**

1 **Registration Step** **Report period:** X Baseline

PLACE ID LABEL HERE

Patient Initials (Last, First) ______________

ECOG Protocol Number ______ ECOG Patient ID ___________

Participating Group Protocol Number ___________ Participating Group Patient ID ___________

Institution/Affiliate ______________

☐ Please mark an 'X' if data have been amended (Please circle amended items in red)

Date(s) Data Amended __/__/____ (M D Y) __/__/____ (M D Y)

☐☐/☐☐/☐☐☐☐ Assessment Date (M D Y)

Section 1

Specify which type of clinician is filling out form

☐ 1=Attending Physician
2=Resident or fellow
3=Advanced practice nurse or nurse practitioner
4=Physician assistant
5=Other, specify____________

Type of contact

☐ 1=No Contact
2=Face to Face
3=Telephone
4=E-mail
5=Web Portal
6=Other

Reason for contact

☐ 1=Routine, on-schedule
2=Off-schedule, unexpected
3=N/A, No Contact

Revised Edmonton Staging System (rESS)

The following items are part of a pain classification system called the Revised Edmonton Staging System (rESS) that is used with the permission of Dr. Robin Fainsinger.

For each of the following features, code the response that is most appropriate, based on your clinical assessment of the patient.

1. Mechanism of Pain

☐ 1=No pain syndrome
2=Any nociceptive combination of visceral and/or bone or soft tissue pain
3=Neuropathic pain syndrome with or without any combination of nociceptive pain
4=Insufficient information to classify

2. Incidental Pain

☐ 1=Absence of incidental pain
2=Presence of incidental pain
3=Insufficient information to classify

3. Psychological Distress and Addictive Behavior

☐ 1=Psychological distress and addictive behavior not present
2=Psychological distress alone present
3=Addictive behavior alone present
4=Psychological distress and addictive behavior present
5=Insufficient information to classify

4. Cognitive Function

☐ 1=No impairment. Patient able to provide accurate present and past pain history unimpaired
2=Partial impairment. Sufficient impairment to affect patient's ability to provide accurate present and/or past pain history
3=Total impairment. Patient unresponsive, delirious or demented to the stage of being unable to provide any present and past pain history
4=Insufficient information to classify.

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E2Z02 Clinician On-Study

Patient Initials: Last ____ , First ____ ECOG Patient ID ____________________

Section 2

How long has the patient had some form of pain?

☐ 1=No current pain problem
2=Less than the past 48 hours
3=Less than the past 1 month
4=More than the past 1 month
5=More than the past 6 months

What treatments or medications are being provided for pain?
(Please code an answer of "01=No", "02=Yes" or "-1=Unknown" for each of the following treatments)

☐☐ Systemic Opioids
☐☐ Non-opioids
☐☐ Opioid/Non-opioid combination
☐☐ Surgery
☐☐ Neuroaxial opioids (epidural or intrathecal)
☐☐ Nerve block
☐☐ Other, specify___________

The patient has pain due to (Please mark an 'X' for all that apply):

☐ Primary disease (cancer)
☐ Effects of cancer treatment
☐ Medical condition unrelated to primary disease
☐ Psychological causes more than actual nociception
☐ Other, Specify_____________________________

Section 3

CONSULTATION: Is patient being referred to another physician or multi-disciplinary team for symptom management?

☐ 1= No
2= Yes

If yes, please code the service(s):

☐☐
☐☐
☐☐

01=Pain
02=Palliative Care
03=Combined Pain and Palliative Care
04=Psychiatry
05=Physical Therapy/Occupational Therapy
06=Nutrition
07=Chaplain
08=Wound/Enterostomal
09=Speech Therapy
10=Practitioner of Complementary Therapy (Yoga, massage, aromatherapy, etc.)
11=Other, Specify_________________
12=Radiation Therapy Service

Please indicate the top 3 areas **in order of importance** that are causing difficulties for this patient as far as you can tell.

☐☐ 1st
☐☐ 2nd
☐☐ 3rd

01=pain
02=fatigue
03=nausea
04=disturbed sleep
05=being distressed (upset)
06=dyspnea
07=cognitive difficulties
08=anorexia/cachexia
09=drowsiness
10=dry mouth
11=sad/depressed
12=vomiting
13=numbness/tingling
14=constipation
15=sore mouth
16=rash/pruritis
17=difficulty walking
18=lack of information
19=financial problems
20=family problems
21=existential worries
22=spiritual problems

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Patient Initials: Last ____ , First ____ ECOG Patient ID ____________________

Section 4

Overall, how much do you think this patient is bothered by <u>difficulties related to comorbidities</u> other than cancer (or the primary disease for which you are seeing the patient)?

☐ 0=Not at all
1=A little bit
2=Moderately
3=Quite a bit
4=Extremely

Overall, how much do you think this patient is bothered by <u>difficulties related directly to cancer</u> (or the primary disease for which you are seeing the patient)?

☐ 0=Not at all
1=A little bit
2=Moderately
3=Quite a bit
4=Extremely

Overall, how much do you think this patient is bothered by <u>difficulties related to treatment of cancer</u> (i.e. chemotherapy or other systemic therapy, radiation therapy, surgery)?

☐ 0=Not at all
1=A little bit
2=Moderately
3=Quite a bit
4=Extremely

Overall, how much do you think this patient is bothered by <u>side effects from medications used to treat pain or other symptoms?</u>

☐ 0=Not at all
1=A little bit
2=Moderately
3=Quite a bit
4=Extremely

Overall, how much do you think this patient is bothered by <u>weight gain or loss?</u>

☐ 0=Not at all
1=A little bit
2=Moderately
3=Quite a bit
4=Extremely

How would you rate this patient's overall quality of life at this time?

☐ 1=Very poor
2=Poor
3=Fair
4=Good
5=Excellent

Relative to other patients with same stage of disease, how would you categorize the degree of difficulty in caring for this patient's physical/psychological symptoms?

☐ 1=Very difficult
2=Difficult
3=Average
4=Easier than average
5=Much easier than average

Investigator Signature ____________ Investigator Signature Date ____________

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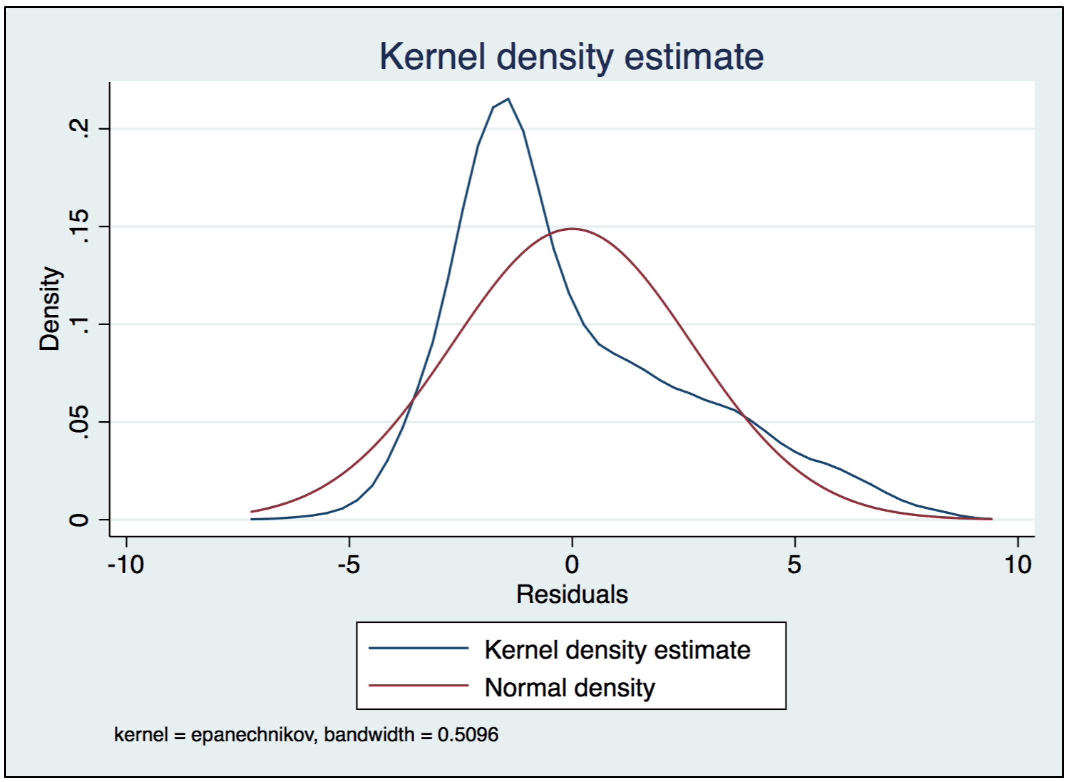
Appendix C: Kernel Density Plot for Specific Aim 1

Specific Aim 1 used linear regression to evaluate the correlates of sleep disturbance severity. (See Section 2.6.2.1 Specific Aim 1: Correlates of Sleep Disturbance Severity.) The following kernel density plot, showing the distribution of residuals in comparison to a normal distribution, is one of several regression diagnostic tests conducted.



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